

MECHANISMS OF HYPERTENSION

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With a Consideration
of Atherosclerosis

By

HENRY ALFRED SCHROEDER, M.D., F.A.C.P

*Associate Professor of Medicine and Director Hypertension Division
Department of Internal Medicine Washington University School
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PREFACE

THE PURPOSE of this monograph is to outline the known and suspected mechanisms which interact to produce a disease and to show how alterations of those mechanisms can lead to specific therapy. When pathogenesis of a disorder is little or well understood not much need be written when partly understood many words cover much ignorance. Knowledge of the basic mechanisms in arterial hypertension is beginning. A volume of this size offers an outline of the known facts and of the hypotheses of best fit past present and future.

We cannot apologize for putting forward working hypotheses which fit the evidence. Far better it is to have them disproven than to attempt no elucidation of mechanisms of disease and thus remain free from controversy—for out of controversy settled comes progress.

In any disorder involving a single mechanism there are many secondary disturbances. Dysfunction of specific organs, general metabolic changes manifest in bizarre and unpredictable signs and symptoms, reactions of the whole and part of the organism to these changes, attempts to reverse them by natural processes. Often these disturbances mislead from rational deductions. Not until the basic pathophysiologic mechanism is understood and treated do the secondary and tertiary manifestations fall into their proper places and carts begin to follow horses. Because arterial hypertension can be successfully controlled, some of its dependant manifestations are better understood. Furthermore, the fact of treatment has led to a strengthening of hypotheses and has pointed out the way to more

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more important of them. Therefore a wide latitude of choice and personal preference was left to the author, who has tried to refer to the pertinent and significant observations with which he is familiar.

The physical vascular factors operating in chronic hypertension are not thoroughly discussed. By and large they are understandable natural consequences and not directly pertinent to the basic problem and its treatment, although they cause most of its death and disability. Statistical correlations of the disease and its effects have also been avoided. Descriptive clinical data does not belong in a book on mechanisms unless they are pertinent to understanding. Nor is the extensive demographic literature listed more than indirectly.

Hypertension as used in this book is a state of generalized vasospasm associated with an adequate cardiovascular apparatus. An arbitrary division of what is hypertension and what is not has been made: a diastolic blood pressure of 90 mm Hg or more is employed as an index of vasospasm. We do not subscribe to one currently popular theory that the diastolic pressure increases normally with age and that levels at age 70 which would be high at 20 are normal. They may be average mean or usual, but they are by no means normal even if they can be shown to do little harm. Just because a disease or a disorder is prevalent in a population does not make it normal. Atherosclerotic plaques in the aorta are not normal although they are almost universal in Western Civilization. As long as healthy human beings can be found on this earth who do not show a progressive degenerative disease linked to age its wide prevalence in other areas makes it be classified as a disease and treated as such.

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CONTENTS

	<i>Page</i>
<i>Preface</i>	vii
<i>Chapter</i>	
I THE COMPLEX OF FACTORS IN THE HUMAN DISEASE	3
Introduction	3
Mechanisms of Some of the Effects of Chronic Arterial Hypertension	13
II BASIC OR CONSTITUTIONAL FACTORS	18
Heredity and Environment	20
Clinical Implications	22
III NEUROGENIC EFFECTOR MECHANISMS	26
Introduction	26
Cerebral Mechanisms	50
Specific Drugs	33
Carotid Sinus Mechanisms	38
Sympathetic Nervous Mechanisms Through Ganglia	39
Sympathetic Nerve Endings	44
Clinical Implications	50
IV NEPHROGENIC EFFECTOR MECHANISMS	55
Evidence for Existence of Other Effector Mechanisms	55
The Nature of the Other Mechanisms	56

CONTENTS

	<i>Page</i>
<i>Preface</i>	vii
<i>Chapter</i>	
I THE COMPLEX OF FACTORS IN THE HUMAN DISEASE	5
Introduction	3
Mechanisms of Some of the Effects of Chronic Arterial Hypertension	13
II BASIC OR CONSTITUTIONAL FACTORS	18
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Clinical Implications	22
III NEUROGENIC EFFECTOR MECHANISMS	26
Introduction	26
Cerebral Mechanisms	30
Specific Drugs	33
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Clinical Implications	50
IV NEPHROGENIC EFFECTOR MECHANISMS	55
Evidence for Existence of Other Effector Mechanisms	55
The Nature of the Other Mechanisms	56

	<i>Contents</i>	<i>xv</i>
	<i>Clinical Implications</i>	200
VII	<i>SOME MECHANISMS IN ATHEROSCLEROSIS</i>	203
	<i>Introduction</i>	203
	<i>Pathogenetic Factors</i>	205
	<i>Some Common Denominators of Hypertension and Atherosclerosis</i>	208
	<i>The Role of Fat and Other Lipids</i>	211
	<i>Clinical Implications</i>	236
VIII	<i>PRACTICAL METHODS FOR MODERN THERAPY OF HYPERTENSION</i>	238
	<i>Introduction</i>	238
	<i>Evaluation of Patient for Drug Therapy</i>	239
	<i>Evaluation of Generalized Vasospasm in Hypertensive States</i>	245
	<i>Specific Use of Drugs</i>	218
	<i>Results Expected</i>	258
IX	<i>A PRELIMINARY APPROACH TO THE TREATMENT OF ATHEROSCLEROSIS</i>	277
	<i>Method</i>	278
	<i>Results Expected</i>	281
X	<i>SUMMARY AND INTERPRETATIONS</i>	284
	<i>Bibliography</i>	297
	<i>Index</i>	329

Clinical Implications	200
VII SOME MECHANISMS IN ATHEROSCLEROSIS	203
Introduction	203
Pathogenetic Factors	205
Some Common Denominators of Hypertension and Atherosclerosis	208
The Role of Fat and Other Lipids	211
Clinical Implications	236
VIII PRACTICAL METHODS FOR MODERN THERAPY OF HY PERTENSION	238
Introduction	238
Evaluation of Patient for Drug Therapy	239
Evaluation of Generalized Vasospasm in Hyper sensitive States	245
Specific Use of Drugs	218
Results Expected	268
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Method	278
Results Expected	281
X SUMMARY AND INTERPRETATIONS	284
Bibliography	297
Index	329

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Chapter I

THE COMPLEX OF FACTORS IN THE HUMAN DISEASE

INTRODUCTION

ARTERIAL hypertension is only a sign of disturbed hemodynamics. At the basis of this disturbance is generalized vasospasm. Without vasospasm the diastolic blood pressure would not rise significantly (1).

Generalized vasospasm is a condition common to a number of hemodynamic disturbances. Whenever effective blood flow through vital organs is reduced a series of reactions is set in motion aimed at restoring flow through those organs at the expense of other less essential ones. Thus vasospasm follows hemorrhage precedes and accompanies shock, severe coronary occlusion, heart failure and other states of circulatory embarrassment. It even accompanies the upright position to a small degree. In these conditions blood pressure is normal or low and effective circulating blood volume and cardiac output low. The vasospasm accompanying the reduction in circulation. Only in late irreversible stages of shock is vasospasm replaced by vasodilatation or its capillary counterparts. If the peripheral circulatory state of vasospasm remained constant and effective circulating blood volume or cardiac output were returned to normal hypertension would ensue.

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blushed rather widely over her face neck and shoulders (there were blotches) when he examined her heart. She appeared a bit timorous and tense but under good self control. Her axillae were wet (or would have been had she not used antisweating preparations) and her hands and feet were cold and moist. She admitted blushing easily in the past on the least provocation. She was excessively neat, regular in her habits almost compulsive but quite unassertive. Laboratory examinations were un revealing. Being curious he immersed her hand in ice water for 1 minute a painful experience she showed no emotion but her blood pressure rose to 168/99 mm Hg falling in 5 minutes to lower levels after it was removed.

This young woman's vascular response to the stress of an examination and to the pain of ice water was almost certainly mediated through the sympathetic nervous system. She was one of those individuals very common in the population who react to stress by vasospasm. Her blushing was characteristic of a diencephalic discharge.

The physician did nothing but suggest an annual physical examination for which she regularly returned. She had two uneventful pregnancies. At the age of 32 her previously labile blood pressure was found to be 160/100 mm Hg or thereabouts not returning to a normal diastolic with rest. As each year passed, a slightly upward trend was observed. At 40 it varied around 180/110 mm Hg. Her mother died of a stroke of apoplexy at the age of 62 which upset her emotionally. She went to another physician who found her blood pressure 200/116 and told her that she had high blood pressure. This was the first she knew of it and she became very agitated. She saw her original physician in an excited state and he measured her blood pressure at 230/140 mm. Her fundi oculi showed spasm but no other changes. He put her in hospital upon which her pressure fell to 160/100 mm measured

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This sequence of events leading to early death can be reconstructed in the light of what is known. For many years this woman reacted to stressful situations by neurogenic vasospasm. Slowly the reversibility of this alteration became less and less some gradually increasing factor being added which maintained a basal blood pressure at higher and higher levels upon which was engrafted a widely fluctuating neurogenic component. This added factor was what killed her. Perhaps she would not have died so early were it not for another disease atherosclerosis which began probably after her menopause and affected her cerebral arteries to such an extent that one ruptured under the high pressure.

2 A man of 25 was found to have a slightly elevated blood pressure and tachycardia when examined for the draft. His mother was hypertensive and his father had died of a coronary occlusion at the age of 51. Enuresis until the age of 8 had occurred but he was free of further urinary symptoms and his urine showed no albumin. He went to his family doctor who found a few bacteria in his urine with about 10 white blood cells per high power field in the centrifuged sediment. repeated cultures showed non hemolytic streptococcus of the colon group in large numbers. He was given phenobarbital and was accepted for duty in the Army. He had a creditable career and won several decorations for bravery. His discharge physical examination showed a blood pressure of 160/100 mm. Not until the age of 31 did he consult a physician for severe headaches and blurring of vision which had appeared a month earlier. His blood pressure was 236/160

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This man suffered from the 'accelerated phase' or what is more exactly and descriptively called malignant hypertension and died young He had the constitutional make up of the hypertensive person to which was added chronic low-grade smouldering pyelonephritis with an organism which does not produce pus but causes scar tissue These two factors operating together shortened his life By the time he died there was little evidence left of the primary renal disease in the kidney distorted by nephrosclerosis

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showed slight reduction with the calculated increased renal vascular resistance on the afferent side of the glomerulus His blood pressure varied moderately but did not fall to normal levels during sleep or the injection of tetra ethyl ammonium chloride Renal "function" was normal He was well working hard and taking few vacations until he was suddenly seized at age 54 with a severe retrosternal pain and was admitted to hospital with an acute coronary occlusion Other than minimal cardiac enlargement a tortuous aorta and the usual signs of infarction there were no abnormalities He recovered slowly but his blood pressure normal or low during his illness became elevated again to 180/110 mm during rest and as high as 220/120 during activity In spite of rearranging his life he remained hypertensive until his second infarction at 57 from which

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She did well but remained hypertensive at home as it was impossible for her to restrict her salt intake and her appetite Not until she was 45 did her first episode of congestive heart failure bring her back into hospital She died 2 years later a cardiac cripple in the interim At autopsy were found arteriolar nephrosclerosis slight to none moderate generalized arteriosclerosis marked cardiac hypertrophy and dilatation (640 Gm.) There was a 1 x 1.2 cm adenoma in the left adrenal cortex.

In her case a functioning adenoma in her adrenal cortex was affecting both her salt and fat metabolism the former influencing her hypertension Better diagnostic methods would have allowed surgical removal

These four cases are illustrative of distinct types of arterial hypertension encountered clinically In actual practice one sees wide variations in their courses and some times bizarre mixtures If the first patient had contracted glomerulonephritis in childhood or pyelonephritis during her pregnancy or had by chance had a link in her ureteropelvic junction due to an aberrant renal artery with stasis and infection she probably would have exhibited more severe hypertension at an earlier age If the second had not contracted pyelonephritis in childhood he might have lived to become hypertensive in his 50's and died of heart failure or apoplexy in his 60's If the renal arterial

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Sequence of Development of Arteriolar Nephrosclerosis This basic lesion which by its very nature can cause renal ischemia and hypertension, is a result of hypertension. In other words the altered hemodynamics of hypertension can lead to a pathologic change which further alters renal and therefore peripheral hemodynamics. The evidence is clear on this point, in rats rabbits dogs and man (Chapter V). Therefore at some point in two of our cases renal vascular disease appeared after hypertension had become well established. Whether or not this secondary disease is responsible for the loss of reversibility of vasospasm is not known, but presumably it is not wholly accountable.

Comment All biological phenomena can eventually be understood in terms of physics and chemistry. The remainder of this monograph is concerned largely with an examination of the biochemical alterations possibly operating to cause this disease which is so eventually fatal as a rule and which is so common to Western Civilization.

MECHANISMS OF SOME OF THE EFFECTS OF CHRONIC ARTERIAL HYPERTENSION

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Sequence of Development of Arteriolar Nephrosclerosis
This basic lesion which by its very nature can cause renal ischemia and hypertension is a result of hypertension. In other words the altered hemodynamics of hypertension can lead to a pathologic change which further alters renal and therefore peripheral hemodynamics. The evidence is clear on this point in rats rabbits dogs and man (Chapter V). Therefore at some point in two of our cases renal vascular disease appeared after hypertension had become well established. Whether or not this secondary disease is responsible for the loss of reversibility of vasospasm is not known but presumably it is not wholly accountable.

Comment: All biological phenomena can eventually be understood in terms of physics and chemistry. The remainder of this monograph is concerned largely with an examination of the biochemical alterations possibly operating to cause this disease which is so eventually fatal as a rule and which is so common to Western Civilization.

MECHANISMS OF SOME OF THE EFFECTS OF CHRONIC ARTERIAL HYPERTENSION

Degree of Peripheral Vasospasm in Chronic Hypertension
The vasospasm can be very intense in chronic arterial hypertension. In fact, it must be so in order to maintain the diastolic pressure at high levels. One can estimate the intensity of the vasospasm by measuring the pressure

seconds after occlusion from 30 to 122 mm Hg (average 65.8 normotension being 15 to 40 average 28.7 mm) a finding surprising on the surface but expected when due consideration is given to hypertensive hemodynamics. The smooth muscle of all arteries and arterioles must therefore be in a state of chronic spasm otherwise hyperemia would occur in those which are not.

Pathogenesis of Hemorrhagic and Exudative Retinitis
The lesions found in the fundi oculi when the diastolic pressure is high are those of edema, hemorrhage, deposits of proteinaceous or lipid material and scarring. Many ophthalmologists consider that hemorrhagic and exudative retinitis is due to localized ischemia of the retina secondary to excessive vasospasm. From a hemodynamic, anatomic and physiologic viewpoint this concept is hardly tenable since a) ischemia of a part does not usually cause edema without infarction b) ischemia does not lead to hemorrhage c) the retinal arteries and arterioles have rather thin muscular coats and d) the lesions appear when the diastolic pressure is high, regress when it is lowered (sometimes to the point of producing retinal ischemia) and occur as a manifestation of a sudden worsening of the hypertension. A more logical explanation is that of plethora or excessive hyperemia. If the artery supplying an area of the retina were diseased so that it could not contract and healthy vessels in the remainder of the body were made to constrict, hyperemia through that diseased vessel would result. Excessive flow and pressure would be transmitted to the capillary bed supplied by that artery. When venous outflow became insufficient to carry off the increased load, water, then plasma and finally red blood cells would be forced through the capillary wall. This concept explains what we find: edema, cotton wool, exudates and hemorrhages. The hard

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This form of reacting to stress may be common to some human beings in many environments and of many races although adequate studies have not been made. The old idea that a part of the population is sympathotonic and part parasympathotonic or vagotonic may have some basis of fact. Different species of animals show different types of reaction to stress: rats, cats, guinea pigs and rabbits not only exhibit opposite types but respond in aberrant ways to known pressor and depressor agents. There are at least two kinds of dogs: nervous overactive breeds which are hypertensive on the first and many subsequent examinations and more or less phlegmatic breeds or cross-breeds which exhibit normal blood pressures and bradycardia (21). There is little reason to believe that the human organism differs radically in its fundamental reactions from those of higher animals.

Sympathotonic people are supposed to be subject to vasomotor phenomena: tachycardia and cardiovascular diseases especially hypertension. Parasympathotonic people are supposed to be subject to bradycardia, a low blood pressure and gastrointestinal disorders especially peptic ulcer. Another type of individual develops allergic reactions. In any population, all varieties and degrees of reactive ability can be expected depending probably on the amount of imbalance between sympathetic and parasympathetic nervous function and the amount of external stress to which individuals are exposed. There may be several different constitutional types: we have not observed true extrinsic asthma in a hypertensive person and such allergic states as hay fever and urticaria are much less common than in the general population. duodenal ulcer is unusual in hypertension although "excess" rheumatoid arthritis and most malignant tumors are seldom encountered in a hypertensive population (22).

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Pickering lately summed up his concepts on the relation of heredity constitution and environment in hypertension (28). To get these conclusions in perspective it may be said that in its mode of inheritance blood pressure resembles height but that the size of the genetic factor is greater in the case of height. However the regression coefficient certainly underestimates the size of the genetic factor since we have been unable to allow for the day to-day variability of blood pressure and we have had to allow for the effects of age by a device which is probably valid when it is applied to large numbers but not so accurate for individuals. By contrast, height shows quite insignificant variations from day to day and for a considerable span of adult existence is uninfluenced by age. The difference between the size of the genetic factor in blood pressure and height is probably less than regression coefficients suggest. Even so it would seem justifiable to conclude that environmental factors are more important than hereditary factors in the pathogenesis of hypertension.

These considerations lead to one further idea which is so revolutionary that I merely lay it before you knowing that your minds must instinctively reject it namely that the current concept of essential hypertension as a specific disease entity is largely an artefact. I venture to suggest that a restatement of the facts would define essen

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An environment considered unfavorable by the individual may be altered by moving to a new one. temporary effects upon the course of moderate and mild stages have been observed. The familiar fall in blood pressure when patients enter the hospital is an example. How permanent this change can be is not known. Minor adjustments in adverse environments especially those caused by other individuals with whom the patient is in close contact may for a time alter emotionally induced stresses (Figure 2).

Drugs especially sedatives have been employed for many years for the purpose of suppressing the emotional tension and lowering the threshold of reactions to stress. As a general rule the more severe the hypertension the less effective are sedative drugs and other such influences upon the disease. Contrariwise the milder the hypertension the more effective are measures aimed at the psyche and the emotional disturbance.

The effects upon the course of hypertension of any one or combinations of the above approaches is directly proportional to the relative influence of these factors in the total picture. Psychosomatic diseases may start as functional derangements mediated through autonomic nerves and end as organic conditions causing death. Therefore while the beginning may lie in the psyche as exemplified by the

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Although Bays and Scrimshaw disagree (32) from all the evidence available we can be fairly certain that hypertension not secondary to renal disease is a disorder fairly well confined to persons exposed to the influences of Western Civilization (4) For example it is unusual in parts of Africa (33) and China (8) very prevalent in American Negroes but rare in American Indians in the Southwest (34) In Uganda only 2.6 per cent of autopsied cases of heart failure were due to essential hypertension the same percentage to atheromatosis and none to coronary thrombosis renal hypertension however, accounted for 16 per cent (35) Surely one is led to conclude that environmental influences are of the greatest importance for in this country probably half the cases of heart failure are hypertensive in origin When viewed from this outlook many discrepancies in the geographic incidence of hypertension fall into line

Comment There are three apparent facts upon which one can speculate

- 1 The predisposition to hypertension is inherited
- 2 There is an emotional overlay in the disease which may be either primary or secondary
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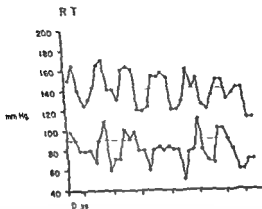


Fig. 9. Daily and nightly fluctuations of supine blood pressure in an 18-year-old man in the prehypertensive phase. His kidneys and heart were normal by all tests. Note that the rise in pressure occurs only during the day. The divisions between each 24-hour period are at midnight.

The evidence against neurogenic effector mechanisms operating in sustained human neurogenic hypertension is poor and usually explicable by an analysis of the cases employed for experimentation or by an understanding of the processes concerned in neurogenic vasoconstriction. At present no one doubts the existence of neurogenically induced vasospasm in man. We must emphasize, however, that in chronic human arterial hypertension the relative parts played by neurogenic and other mechanisms vary considerably from patient to patient (Chapter IV). The contrary evidence follows.

1. Little or no increase in urinary catechol amines is usually found (11). Norepinephrine, however, is liberated at nerve endings and metabolized or conjugated *in situ* before its products reach the blood stream. Therefore overproduction must be great enough to saturate oxidative and conjugative enzymes in order to allow enough to spill

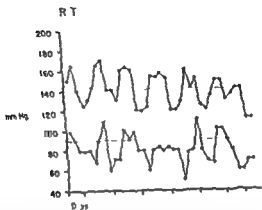


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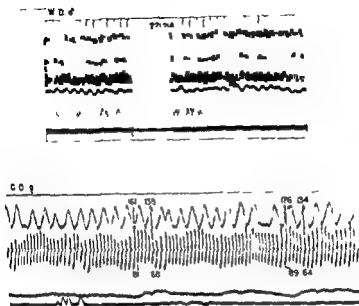


FIG 4 Spontaneous variations in blood pressure measured photokymographically by direct arterial puncture W G normal and normotensive variation 9.6 mm Hg F T normotensive convalescent from severe acute poliomyelitis with probable slight involvement of the hypothalamus or medulla giving rise to neurogenic vasomotor instability variation 41/20 mm Hg W D fairly severe nephrogenic hypertension variation 13/1.4 mm Hg I H severe neurogenic hypertension variation 3.2/2.0 mm Hg W D (repeat after several days rest) variation 7.5 mm Hg C O mild neurogenic hypertension variation 49/19.5 mm Hg Bi indirect measurement C O a systolic pressure when taken by a white coated physician varied from 180 to 240 mm and her diastolic from 120 to 100 mm nurses always obtained readings 20 to 30 mm lower The wide fairly regular tracings are those of respiration the smaller ones of a plethysmograph on the finger Camera speeds 125 mm and 25 mm per second

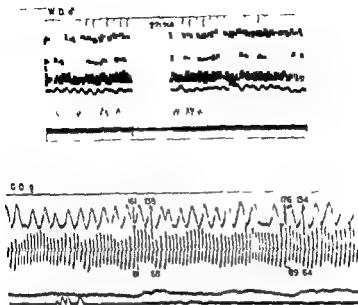


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There are four possibilities to explain the cerebral role in human hypertension. 1 The nervous temperament of the hypertensive person with the frequent finding of anxiety and frustration may initiate repetitive discharges through the sympathetic nervous system. Subnormal assertiveness, obsessive-compulsive traits and anxiety are said to be common to the hypertensive personality (26, 27). This hypothesis has always been an attractive one but is unproven and most difficult to investigate with the tools at hand.

2 The peripheral metabolic abnormalities associated with hypertension may cause stimulation of cerebral metabolism. It is known that many primary amines cause central excitatory effects. Amphetamine (Benzedrine) is a good example. In fact Mann and Quastel (57) suggested that the central stimulant action of *dl* phenylisopropylamine (Amphetamine) is related to its inhibition of tyramine oxidation by amine oxidase in brain. On this basis Fellows and Bernheim (58) examined a large number of structurally related salts in rats and found in many instances good correlations between central stimulation and cerebral amine oxidase inhibition. Clinically the excitatory actions of epinephrine and a number of derivatives are well known. We have observed profound and

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SPECIFIC DRUGS

Whatever the cause of the increased nervous excitability of hypertensive patients many agents have been used to counteract it and thus produce variable effects upon blood pressure depending upon a) the relative part played by the brain b) the effectiveness of the drug and c) the ability of the patient to tolerate side effects Sedatives have been used for many years in an attempt to allay tension and anxiety They will not be discussed since their employment is wide

Serotonin Antagonists Reserpine causes depletion of cerebral serotonin in the experimental animal (65-66) platelet serotonin is also reduced to a low level. The net effect of this agent, a chemical analogue of yohimbine, is to produce an effect the equivalent of a prefrontal lobotomy (67). Its locus of action appears to be prehypothalamic and subcortical, the posterior hypothalamus wherein lie the sympathetic centers, is partially blocked (68). The effect of the drug is cumulative, requiring a week or two for oral doses to act maximally, although rapidly excreted, the drug itself leaves serotonin receptors in the brain blocked for long periods. Aside from its 'tranquilizing' action, however, it has been reported that it has caused gastric acidity and that it has appeared de novo or become activated in one of our cases of chronic ulcerative colitis has developed (69). Various cerebral symptoms are

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TABLE 1—(continued)

	Reserpine (123 subjects)	Chlorpromazine (137 subjects)
Epistaxis	2 4	1
Blurred Vision	0	1 5
Dry Mouth	0	1 5
Heart Burn	0	1 5
Edema	7 3	5 1
Pruritus	1 6	1 5
Dermatitis	0	9 5
Jaundice	0	5 1
Hepatomegaly	0	2 2

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Other antemetabolites to serotonin are not used in hypertension: yohimbine because of its nephrotoxicity and diisergic acid diethylamide which produces schizophrenic-like states (63-66). The most interesting are the nitroindoles which are true competitive antagonists blocking

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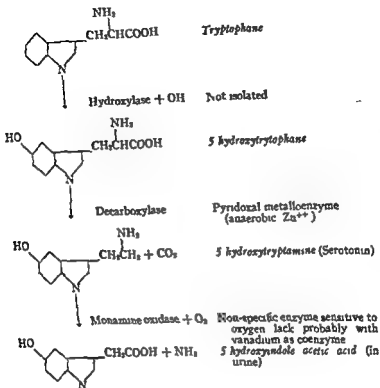


FIG 5 Metabolism of serotonin, modified from Sjoerdsma *et al* (61)

phane and its decarboxylation (Fig 5) The hydroxylase has not been discovered but the renal decarboxylase (71) contains a pyridoxal metal complex as a coenzyme (72) like many other amino acid decarboxylases. Serotonin is metabolized by monamine oxidase (Chapter IV) an enzyme requiring oxygen and sensitive to oxygen tension. Therefore renal ischemia could allow the formation of serotonin by anaerobic decarboxylation but prevent deamination *in situ* due to oxygen lack. Serotonin would then escape into the blood and be deaminated either in the lungs or on arterial smooth muscle. While it is doubt

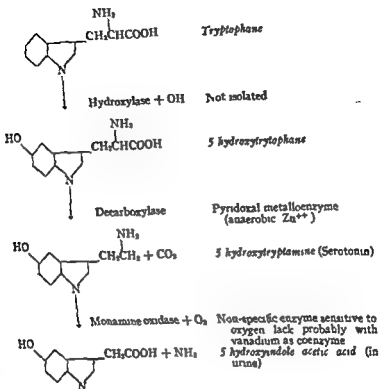


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phane and its decarboxylation (Fig 5) The hydroxylase has not been discovered but the renal decarboxylase (71) contains a pyridoxal metal complex as a coenzyme (72) like many other amino acid decarboxylases. Serotonin is metabolized by monamine oxidase (Chapter IV) an enzyme requiring oxygen and sensitive to oxygen tension. Therefore renal ischemia could allow the formation of serotonin by anaerobic decarboxylation but prevent deamination *in situ* due to oxygen lack. Serotonin would then escape into the blood and be deaminated either in the lungs or on arterial smooth muscle. While it is doubt

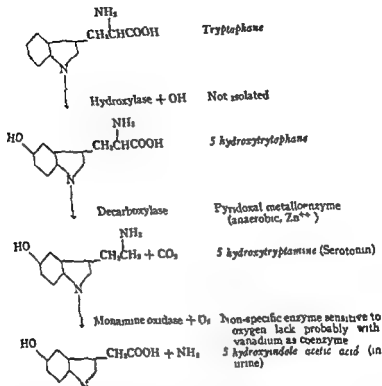


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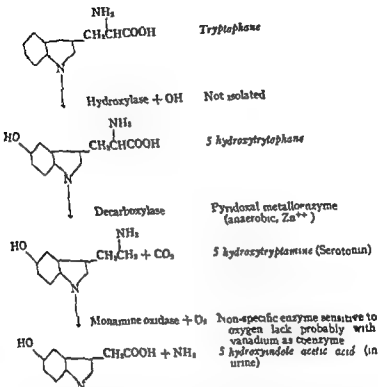


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A and B are the most purified alkaloids usually found in a mixture and most difficult to separate. They cause depression of blood pressure and bradycardia, nausea and vomiting may result from vagal stimulation (79). The pathway is through the glossopharyngeal nerve to the vasomotor center (78). When doses are adjusted properly, intermittent normotension can result from the careful use of protoveratrine and its impure derivatives (80). Apparently tolerance is quick to appear and disappear so that sustained normotension will not result unless adjuncts operating on other mechanisms are used. Whether or not this drug is a true antihypertensive agent affecting the basic process is unclear although the hemodynamic response is quite favorable (Table II).

Baroreceptor Changes McCubbin, Green and Page (81) have recently shown that the carotid sinus and aortic depressor mechanisms are set at a higher level of pressure in renal hypertensive dogs than in normotensive dogs. They propose (the ingenious theory that this higher setting maintains the hypertension) even when the initiating mechanism (renal ischemia, pheochromocytoma, toxemia of pregnancy) is removed. Thus (renal hypertension slowly becomes neurogenic) buffer nerve hypertension as Ogden has suspected in rats (82). If this were so in man one would expect that late chronic hypertension would respond to the use of drugs or surgery acting on nerves better than would early hypertension. Clinically the opposite holds true; therefore this attractive hypothesis necessarily can be discarded as applying to most human cases.

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The ganglion itself governs the integrity of the post ganglionic fibres much as the spinal nuclei control the integrity of their neurons. Removal of a ganglion is probably followed by degeneration of the nerve after a few days sensitivity of the nerve ending to circulating vasoconstrictor substances develops. Therefore in order to perform an adequate sympathectomy preganglionic fibres must be cut.

Specific Drugs Chemical ganglionic blocking agents usually contain quaternary ammonium stabilized tetra covalent nitrogen competing with acetyl choline or other more labile nitrogenous substances. Numbers of such compounds exist. The simplest one of the group is tetraethyl ammonium ion known for many years as a vasodilating drug of short action. Longer action is achieved by lengthening the carbon chain and doubling the nitrogen group (pentamethonium pendiomide hexamethonium) or by adding cumbersome ring structures (pentolinium chlorisondamine). All act in a similar manner differing only in duration of action and degree of gastrointestinal absorption. A new blocking agent mecamylamine (Inversine) differs considerably in structure being a complex spatial molecule with trivalent nitrogen as a secondary amine. It has the advantage of virtually complete absorption from the gastrointestinal tract (83). Comparative doses are shown in Table III (Fig 6).

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TABLE III
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Ion	Usual Effective Oral Dose		Maximum Tolerated Oral Dose		Duration of Action of Oral Drug hrs	Usual Effective Parenteral Dose†
	Single Dose mg	Daily Dose mg	Single Dose mg	Daily Dose mg		
Tetraethyl Ammonium	†	†	†	†	1-1	500
Pentamethonium	500	2500	†	†	3	25
Hexamethonium	500	2500	1000	6000	4	25
Pentolinium (Ansohsen)	100	500	800	4000	4-5	25
Chlorthalidamide (Ecosid)	50	250	200	1000	4-6	15
Mecamylamine (Inversine)	10	50	25	150	4-8	10

* When combined with hydralazine

† Sublingual doses effective oral not

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"picture" caused by norepinephrine secreting pheochromocytomata. Therefore the neurogenic component of hypertension can be considered to be mediated by this substance.

Norepinephrine is derived either from dihydroxyphenylserine by decarboxylation or from tyramine by hydroxylation of the benzene ring and the β -carbon. The first appears the most facile method for the nerve ending to make this substance rapidly. It is inactivated either through conjugation through oxidation of the amine nitrogen by monamine oxidase or by rearrangement of its molecule to form an indole nucleus through oxidation by polyphenol oxidase, a copper enzyme.

The ideal agent for counteracting norepinephrine has not been found. There are a number of sympatholytic drugs which inhibit its action on nerve endings and which are effective for short or longer periods in experimental animals. We list them only as directions for research. These may be grouped roughly as derivatives of benzylamine, of phenethylamine, of ergot, of benzodioxane, and of imidazole (Table IV, see page 48). All contain tertiary substituted nitrogen.

Derivatives of Benzylamine. Dibenzamine, a complex structure remotely related to norepinephrine, forms tight bonds at sympathetic nerve endings, preventing the action of this constrictor substance, probably by competitive inhibition. The action is prolonged for many hours. It is moderately effective by mouth, much more so intravenously. There are many side effects in man, especially on the brain. Dibenzamine and its relatives are the most effective sympatholytic agents known at present, but their value in hypertension remains to be proven.

Derivatives of Phenethylamine. We had an opportunity of testing a group of primary amines in rats for sympath

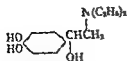
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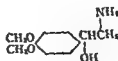
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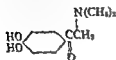
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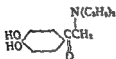
SKF 1297 A



SKF 1277 A



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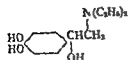


SKF 1300-A

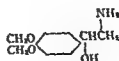
Renal hypertensive dogs responded by a lower diastolic pressure only when SKF 1298-A was given * SKF 690 A was a powerful epinephrine like substance in man causing vasodilatation and an increased cardiac output with fall in diastolic pressure SKF 1298-A caused symptoms suggestive of cholinergic stimulation two others were without effect

The experiments of Furchgott are of interest Using the spirally cut rabbit's aorta as a source of smooth muscle he was able to show on this simple system how certain agents such as dibenamine block all constrictor amines others block some and others block only a few (85) Therefore it is likely that very specific agents can be found which will pick out one primary amine and not others for inhibition

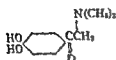
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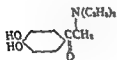
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Derivatives of Imidazole Tolazoline (Priscoline) and Phentolamine (Regitane) are two short acting moderately effective adrenergic blocking agents containing both benzene and imidazole rings. Phentolamine while opposing the actions of both epinephrine and norepinephrine is useful for the most part only as a test substance for circulating catechol amines. It usually causes a transient fall of blood pressure in hypertensive patients suggesting that some sympathetic tone is present. In azotemia the effect may be prolonged and profound. Cardiac stimulation is the rule. Tolazoline is readily absorbed and excreted unchanged in the urine; phentolamine is apparently metabolized up to 90 per cent of the dose. The short durations of action limit their use.

The Benzodioxanes Piperoxan (Benodaine) and pro-sympal first synthesized by Fourneau act transiently usually by vasoconstriction. They do oppose however the action of epinephrine probably by competitive inhibition; norepinephrine is blocked only by toxic doses. Side effects are many especially smooth muscle stimulation and limit their use except in epinephrine producing pheochromocytomas.

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The toxic or side reactions of reserpine and chlorpromazine have been given in Table I. The most serious late toxic reactions of reserpine are those of agitated depressive psychosis which are often accompanied by suicidal tendencies and may lead therefore to death. Of chlorpromazine there are hepatic disease and granulocytopenia some 17 deaths have resulted (92). Chronic administration of any drug given to control not cure a chronic disease may back fire. Furthermore in severe hypertension the use of mild drugs is potentially dangerous giving the physician a sense of security while the disease continues relentlessly on its ravaging course.

There are no known late toxic reactions to protoveratrine. Immediate side effects are those attributable to vagal stimulation i.e. nausea and vomiting. The rapid development of partial tolerance in a few hours with restoration of sensitivity after a few hours rest is unexplained.

Ganglionic blocking agents show many side effects most of them the result of parasympatholysis or sympatholysis (Table V). Only two serious ones of this nature have been encountered. The first occurs when partial often asymptomatic obstruction to a hollow organ has been present. Complete obstruction may result. The second is concerned with the mode of excretion. Absorbed blocking agents are excreted in the urine. If severe renal disease is present ganglionic blockade may cause hypotension and anuria as the drug is then excreted in the urine.

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Ganglionic blockade disease occurs in poorly treated malignant hypertension (93-94-5). It is characterized by excessive tachypnea worsened in the sitting or standing position, diffuse or patchy roentgenologic changes in the lungs with few physical signs and interstitial pulmonary fibrosis at autopsy. Almost all cases have exhibited azotemia (5). The microscopic findings are indistinguishable from uremic pneumonitis. One patient recovered after the use of cortisone; the remainder died.

All of the antihypertensive agents with powerful actions can induce cardiovascular accidents due to the nature of the arterial disease (atherosclerosis) often encountered and too sudden alteration of hemodynamics. Arterial thrombosis is the most serious although it is rare. Such reactions are not true side effects of the drugs themselves but are inherent dangers of their overenthusiastic and careless use.

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Chapter IV

NEPHROGENIC EFFECTOR MECHANISMS

EVIDENCE FOR EXISTENCE OF OTHER EFFECTOR MECHANISMS

To this point we have inferred that mechanisms other than neurogenic account for much of the generalized vasospasm seen in severe hypertensive states. Although their natures are imperfectly understood, there is sufficient experimental and clinical data to warrant careful examination of several hypotheses which fit or do not fit the facts.

Most of the evidence for the existence of effector mechanisms other than neurogenic comes from experimental hypertension and from the wide variations in the acute or prolonged effects of drugs acting on sympathetic nerves. To take up the pharmacologic evidence, the following clinical observations are pertinent:

1. Early and mild hypertension responds well to simple measures and milder acting sympatholytic drugs; severe hypertension little or not at all.

2. Extensive surgical sympathectomy, either lumbar or subtotal, still leaves a sizeable proportion of patients as hypertensive as before; relieves a fair number completely; with the remainder improved to variable degrees.

3. Full therapeutic doses of ganglionic blocking agents or phentolamine cause intermittent or sustained normotension in a few cases; a modified response in many; and no appreciable effects (other than postural ones) in the more severe forms of hypertension.

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3. Full therapeutic doses of ganglionic blocking agents or protoveratrine cause intermittent or sustained normotension in a few cases; a modified response in many; and no appreciable effects (other than postural ones) in the more severe forms of hypertension.

vasoconstrictors themselves or which inhibit the destruction of normally circulating pressor substances

b) Some organ is not destroying or excreting pressor substances normally present, so that they accumulate and form a new homeostatic level

c) Some organ is sensitizing the blood vessels to normally circulating pressor substances

d) For some reason the arterial and arteriolar walls become edematous thereby increasing peripheral resistance.

Probably all of these mechanisms can operate under different clinical circumstances

The vast experimental and large clinical experience with hypertension induced by renal ischemia focuses attention upon the kidney as a mediating mechanism for that component of elevated arterial pressure which is not neurogenic in origin. The posterior pituitary however forms a pressor substance and the adrenal cortex can sensitize blood vessels to vasoconstriction therefore endocrine mechanisms must also be considered (Chapter V). In this section we are concerned however with nephrogenic mechanisms

First the effects of sympathetic nervous discharges upon the renal circulation must be examined. Both emotional tension and catechol amines cause renal vasoconstriction abolished in the case of the former by sympathectomy. Curiously enough norepinephrine constricts in so far as is known only the renal circulation to a greater extent than other vascular beds. The hemodynamic profile is similar to that seen in hypertension with efferent arteriolar constriction being dominant. Epinephrine produces the same renal profile. Therefore increased neurogenic sympathetic tone can cause relative renal ischemia but ischemia of no other known organ

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4 No renin or angiotensin can be found after several weeks of hypertension although the enzyme is present at first VEM in blood however increases with time to a plateau (103)

5 The oxygen consumption of the kidney may be reduced (104)

In kidneys removed from hypertensive rats and dogs the following enzymatic alterations have been demonstrated

1 Amino acid oxidation is reduced (104 105) suggesting a general inhibition of oxidative enzymes

2 Transamination is reduced in the presence of adequate pyridoxal phosphate (104) suggesting a depletion from renal tissue of apotransaminase

3 Deamination of amines is reduced (104) suggesting depletion of monamine oxidase

4 Succinic dehydrogenase and possibly cytochrome oxidase are reduced (105) All of these enzymatic alterations can be explained by loss of renal tissue consequent to prolonged ischemia

✓ In man the following changes have been measured

1 Renal oxygen consumption is usually reduced (106 107) reflecting the ischemia

2 The urine is usually acid (108) reflecting perhaps the acidity of the cortex in ischemia

3 There is a tendency for renal loss of sodium and some chloride (109 110 4) caused in the case of sodium possibly by the acidity producing loss of base

4 The ratio of ammonia to titrable acid is lower than normal influencing possibly the sodium losing tendency of hypertensive kidneys (111)

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This is more than an academic point. If hypertension were the result of chronic inhibition of a renal enzyme, removal of the enzyme or removal of the kidneys would accomplish the same result. The next question is whether a precursor is altered by ischemic kidney into a pressor

G. J. & W.

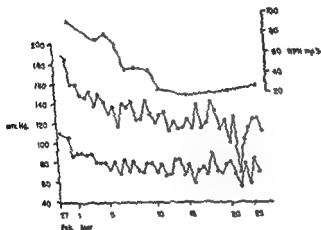


FIG. 7 Azotemic hypertension with reversal when azotemia regressed. Patient was a 45-year-old woman with abdominal lymphosarcoma which had involved both ureters causing bilateral hydronephrosis. It was impossible to pass a urethral catheter through the left. Radiotherapy was instituted, resulting in a shrinkage of the tumor, a return of renal function toward normal and a fall of blood pressure occasionally to hypotensive levels.

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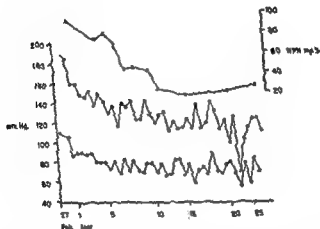


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TABLE VI
AMINO ACIDS CAPABLE OF FORMING URINARY AMMONIA*

Amino Acid	Renal Amino Acid Oxidase Present	Renal Diaminase Present	(Dog and Rat)	
			Renal Decar- boxylase Present	Renal Amine Oxidase Present
Glycine	+			0
L-Alanine	+			
L-Leucine			+	+
L-Cysteine			+	?
L-Methionine			?	?
L-Aspartic Acid	?		?	?
L-Asparagine				
L-Glutamine		+		
L-Histidine			+	+
Oxygen required for enzyme	+	0	■	+
No ammonia formed by glutamic acid lysine or arginine				

After Meister (432)

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Both of these enzymes are found widespread throughout many tissues. The liver is a rich source. Smooth muscle and gut contain them. Their ubiquitous nature is all out of proportion to their known metabolic functions.

The most interesting aspect of monamine oxidase in reference to renal ischemia is its sensitivity to oxygen lack (Fig. 8). Small decrements of oxygen tension inhibit enzymatic activity considerably which is not always the case for other oxidases (89). If this relationship holds in

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Bacteria in the colon have the proper decarboxylating enzymes for these amino acids and for several others. The resultant amines should theoretically act on the vascular system and brain in a similar manner if absorbed. That they do not usually so act can be explained by their destruction by amine oxidase in intestinal wall and in liver. For it is well known that primary amines and even epinephrine can be ingested in large quantities without systemic effects, adding one or more methyl groups to their side chains as in amphetamine or ephedrine, however prevents oxidation by hepatic and intestinal amine oxidase allowing the drug to pass unchanged through liver and act on brain or blood vessels. No orally active amine vasoconstricting agent lacks this side chain. It is possible however that when bacterial flora are selectively inhibited by antibiotics products of intestinal putrefaction can be absorbed into the circulation from the lower colon and cause symptoms especially when the liver is damaged.

The fact that extracts of arterial hypertensive blood usually contain more primary amines than those of normotensive blood (90-91) and that certain new or abnormal

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✓ Since we are concerned primarily with the killing factor in hypertension and not with mild neurogenic vasospastic states it is well to examine the properties of this enzyme system further. There are two which are of help in implicating a disturbance of amine oxidation. First of all amine oxidase acts on hypertensin or angiotonin (4, 112). This pressor amine is a complex polypeptide (119). Second the enzyme acts on pherentasin. This pressor amine is probably a polypeptide (120). If the enzyme can act on terminal amines of peptides it is possible that the formation of such peptidic amines occurs through decarboxylation and destruction by terminal amine oxidation. Therefore we cannot exclude monamine oxidase in any theory of pathogenesis.

This enzyme probably needs vanadium as a cofactor. Vanadium occurs in three valence states and is therefore a good metal for oxidation reduction reactions being used as such by certain ascidia which concentrate it from sea water. While not shown to be an essential trace element for man, vanadium is found in tissues of mammals and occupies a place in the periodic table where essentiality might be inferred. This subject will be discussed further in Chapter VI.

Possible Role of the Lungs. In order to cover other conceivable mechanisms of vasospasm induced by humoral pressor substances we cannot neglect the pulmonary circulation. Any vasoactive material formed in an organ and discharged into the venous circulation must pass through the lungs before entering the area of action, the peripheral arterial bed. The lungs destroy at least one vasoactive

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TABLE VIII
COMPARISON OF PROPERTIES OF ANIMAL HYPERTENSIN AND
HUMAN PHERENTASIN

Inactivation by	<i>Hyper-</i> <i>tensin</i> (I)	<i>Pheren-</i> <i>tasin</i> (II)	Method and Remarks
Drying	0	+	(1) can be lyophilized
Heat at pH 8.8	+	+	
Heat at pH 2.0	0	0	
Nitrous acid	+	+	
Nitrohydrazine	+	+	
Semicarbazide	?	±	(2) alters to a rapid reactant
Hydroxylamine	?	±	(2) alters to a rapid reactant
Amine Oxidase	+	+	
Tyrosinase	+	0	
Papain + cysteine	+	+	
Chymotrypsin	+	0	
Carboxypeptidase	+	0	
Trypsin	+	0	
Pepsin	+	0	
Mg ⁺⁺	0	0	
Mn ⁺⁺	+	+	(1) rapid (2) slow
Cr ⁺⁺	?	0	
Co ⁺⁺	+	±	(1) rapid (2) partial
Fe ⁺⁺	0	0	
V ⁺⁺⁺	~	~	Both enhanced
Cu ⁺⁺	0	0	
Zn ⁺⁺	0	0	
Hydralazine	+	+	(1) more sensitive
NaSCN	+	+	
8-Hydroxyquinoline	+	+	
EDTA Na ₂ H ₂	0	±	(1) slow (2) more rapid
Na ₂ S ₂ O ₄	+	+	(1) 50% in 22 hours
Na ₂ Fe(CN) ₆ NO	+	+	(2) 50-100% in 3-6 hours
1 benzyl 2 methyl 5 methoxy tryptamine	+	+	Rapid for both
			Serotonin antagonist

NOTE: While distinct differences between these two substances are obvious the hypertensin used was probably principally hypertensin I (angiotensin) obtained from hog renin and serum Pherentasin may be hypertensin II of human origin with a slightly different structure since there is no reason to believe that the α globulins of pig and man are identical.

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Cr ⁺⁺	?	0	
Co ⁺⁺	+	±	(1) rapid (2) partial
Fe ⁺⁺	0	0	
V ⁺⁺⁺	-	-	Both enhanced
Cu ⁺⁺	0	0	
Zn ⁺⁺	0	0	
Hydralazine	+	+	(1) more sensitive
NaSCN	+	+	
8-Hydroxyquinoline	+	+	(1) slow (2) more rapid
EDTA Na ₂ H ₂	0	±	(1) 50% in 12 hours (2) 50-100% in 3-6 hours
Na ₂ S ₂ O ₄	+	+	
Na ₂ Fe(CN) ₆ NO	+	+	Rapid for both
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Vasoexcitor Material This unidentified substance has the property of sensitizing blood vessels to epinephrine when the latter is topically applied It comes from ischemic kidney and is active in minute amounts Larger quantities appear in chronic hypertension and congestive heart failure (100) Other substances such as renin pherentasin sustained pressor principle and some primary amines also have this property which may be nonspecific

Others A great many vasoactive substances have been found in urine and blood most of them eventually showing up as primary amines or more complex structures They may represent metabolic by products of the basic renal abnormality No good case for any has been proven as directly concerned in chronic generalized vasospasm (133-135 112 4)

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Reaction A would thus occur in acute vasospastic states while reactions B C or D might take place in chronic states Pherentasin needs no serum for activity that it has at least six amino acids is based upon the findings of the active material showing six spots in chromatograms A more unitary hypothesis is that pherentasin is actually hypertensin II, a matter on which we have no evidence as yet

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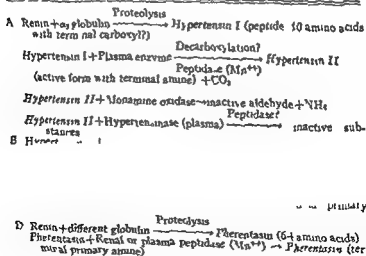


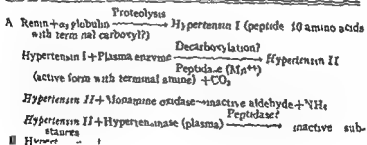
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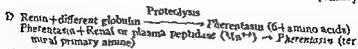


Fig 9

to do more than detect the grosser lesions. A disease causing renal ischemia which then influences hypertension is often unsuspected because the cardiovascular manifestations of the elevated blood pressure may mask the underlying renal abnormality.

Organic Parenchymal Renal Disease. The most common diseases of the kidney producing ischemia are pyelonephritis and glomerulonephritis.

(143) The latter may be masked insofar as the urinary sediment is concerned by the superimposed hypertension. To list the other more unusual renal diseases congenital or acquired is hardly within the province of this discussion; most are often but not always associated with hypertension (144, 4).

Organic Extra renal Arterial Disease. Atherosclerosis of the mouths of the renal arteries is common in generalized and in aortic atherosclerosis. The mechanism for the deposition of lipid in plaques about the orifices of bifurcating arteries is not known. Undoubtedly pressure changes play a part; possibly the presence of increased numbers of vasa vasorum at such bifurcations influence the lesions. Therefore when atherosclerosis involves the renal arteries partial renal ischemia may result with subsequent elevation of the blood pressure in predisposed individuals. With aortography becoming more common such lesions are more frequently demonstrated. According to Blackman they are the usual findings in hypertensive patients (145). It is possible that they represent the

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Organic Intra renal Arterial and Arteriolar Disease The almost universal lesion found in the kidneys of patients with hypertension at necropsy is renal arterial and arteriolar sclerosis. This lesion is not the cause of the hypertension however but is the result. And a late result at that. About 50 per cent of patients having renal biopsies done during the operation of lumbodorsal sympathectomy had little or no arterial or arteriolar sclerosis (159). This lesion has been shown to result from hypertension produced by a variety of causes in rats (160-163) rabbits (164) and dogs (165-7). Serial renal biopsies in dogs over a seven year period have demonstrated the gradual development of the lesions only after 2 to 4 years of both neurogenic and unilateral renal hypertension the first sign being a thickening of the glomerular capsule and later an increase in material in the glomerular tuft staining with periodic acid (7).

None of these renal diseases alone can be said to cause hypertension in man until azotemia develops. Hypertension is absent in 30 to 50 per cent of patients with the first two types in non azotemic stages. The third type of course is the result of hypertension. They do however influence it profoundly and may often alter its course to a progressive and severe one. That quality which we call the ability to react to stress by vasospasm must apparently be present first and in conjunction in order for severe sustained hypertension to develop in patients with organic renal ischemia.

Why then are there no more cures of hypertension

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matter of fact many effective drugs bind metals in one way or another (Chapter VI) This common property immediately focuses attention on metalloenzymes in kidney and vascular smooth muscle It also stimulates considerable thought about the role of trace metals in pathogenesis of severe hypertension in which the neurogenic component has become of minor consequence

The agents used in man are hydralazine and its derivatives thiocyanate ion sodium nitroprusside 2,3-dimer captopropanol (BAL) sodium azide and ethylenediamine tetra acetate Of practical interest for continuous use are only the first three the effects of the other three being short lived (Table X)

HYDRALAZINE AND OTHER CHELATING AGENTS

Hydralazine and its derivatives are unique drugs No other agents known produce the same actions on vascular smooth muscle

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etiology of s

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Chemical Reactions Hydralazine like other hydrazides is a strong chelating agent. It will form a complex with iron copper tin vanadium, manganese nickel silver and mercury The possible structure is



making a five sided ring with nitrogen a most stable chelate This property is shared by isonicotinic acid hydrazide (isoniazid) and probably its isopropyl derivative

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(iproniazid) whose pyridine bases in themselves weakly bind metals without the hydrazide group (Table XI) Distinct specificities for metals are exhibited however

Hydralazine is also a carbonyl reagent as are some other hydrazides phenyl hydrazine for example which forms an ozonone with glucose It will bind pyruvate acetate and acetaldehyde (168) Hydralazine has specific reactions in that no ozonone is formed with glucose or lactic acid It does not combine with any of the steroids tested (168) It is 1 hydrazinophthalazine (Apresoline)

This agent also complexes with the sulfhydryl groups on cysteine glutathione 2 3-dimercaptopropanol (BAL) and other simple mercaptans The complex can be dissociated readily by arsenic

TABLE XI A
ISONIAZID * HYDRALAZINE AND METALS

	Isoniazid		Binding of Hydral- azine† + Me ⁺⁺	Similarities
	Destruction by Me ⁺⁺ Auto- claving %	Destruction by Me ⁺⁺ H ₂ O ₂ %		
Mg ⁺⁺	0	5	0	+
Ca ⁺⁺	0	5	0	+
Mn ⁺⁺	100	100	87	+ Greatest at pH 6.5-7.0
Fe ⁺⁺	50	80	22	
Fe ⁺⁺⁺	10	95	100	+
Co ⁺⁺	40	35	0	
Ni ⁺⁺	10	15	48	
Cu ⁺⁺	100	100	100	+ Greatest at pH 9.5-10.0
Zn ⁺⁺	15	15	0	±

Lewin E. and Hirsch J. G. Studies on the stability of isoniazid. *Am Rev Tuberc & Pulm Dis* 71:732 1955

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Ca ⁺⁺	0	5	0	+
Mn ⁺⁺	100	100	87	+Greatest at pH 6.5-7.0
Fe ⁺⁺	50	30	22	
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TABLE XII

INHIBITION OF HISTAMINASE BY HYDRAZIDES

Substance	Concentration Producing 50% Inhibition (molar)	Antihyper- tensive Effect
Guanidine HCl	10^{-3}	0
Thiosemicarbazide	10^{-3}	+
Semicarbazide HCl	5×10^{-3}	?
Hydrazine SO_4	8×10^{-3}	?
Amino-guanidine HCO_2	5×10^{-3}	0
1-4 dihydrazinophthalazine	2.3×10^{-3}	+
1 hydrazino-4 methylphthalazine	2.5×10^{-3}	+
1 hydrazinophthalazine	6×10^{-3}	+

Gross F Schuler W Tripod J and Meier R Inhibition of diaminoxidase (histaminase) by phthalazine derivatives *Experientia* 8 229 1952

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It binds strongly to arterial mash serum proteins egg albumin and some polypeptides possibly through carbonyl or sulphhydryl linkages It does not bind with casein nor with mixed amino acids

Enzymatic Reactions Hydralazine is also an anti-enzyme for several known systems It and its derivatives are strong antihistaminases theoretically preventing histamine formed from histidine from being destroyed rapidly but not necessarily causing release of histamine from histidine (Table XII) Histamine can come from the action of histidine decarboxylase believed to be a pyridoxal enzyme if so inhibition by hydralazine might be suspected Hydralazine is a potent inhibitor of DOPA decarboxylase in small concentrations also a vitamin B_6 enzyme (Table XIII) There is some evidence that histaminase itself may be a pyridoxal enzyme (169)

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TABLE VIII—(continued)

Substance	DOPA Decarboxylase M ₅₀ of agent				Monamine Oxidase (Substrate tryptamine) M ₅₀ of agent			
	10	1	0.1	0.01	10	1	0.1	0.01
Isotiazid	41	84	99	100	75	98	103	101
Iproniazid	108	—	—	—	14	52	91	101
Pyridoxal Isoniazid	100	114	92	91 (90)	96	101	101	101
1,5-diphenyl-3-thiocarbonylhydrazide	100	97	—	—	—	—	—	—
8-hydroxyquinoline sulfonic acid	102	—	—	—	105	—	—	—
Reserpine	102	90	92	94	—	—	115	95
β -Mercaptopropionic acid	81	98	100	97	123	111	103	—
Tetrasodium pyrophosphate	80	101	97	—	95	—	95	97
Sodium cyanide	66	85	98	97	45	98	—	—
Sodium thiocyanate	89	98	100	110	100	—	—	94
Sodium azide*	91	94	—	—	115	116	98	101
Choline azide	100	—	—	—	112	104	101	100
Sodium Nitroprusside*	63	71	76	91	129	98	101	—

Italicized figures represent 20% change at 1.0 millimolar concentrations or less considered significant

Those in parentheses show further dilutions by 10

* Antihypertensive in man. Note that some of these tend to depress one enzyme and enhance the other

TABLE VIII—(continued)

Substance	DOPA Decarboxylase Multimolarity of agent				Monoamine Oxidase (Substrate tryptamine) Multimolarity of agent			
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Sodium cyanide	66	85	98	97	45	98	—	—
Sodium thiocyanate	89	98	100	110	100	—	—	94
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TABLE XIV B

EFFECT OF ADMINISTRATION OF HYDRALAZINE ON URINARY
EXCRETION OF 4-PYRIDOXIC ACID (MG) (111)

	No Sbjcts	No Tests	Mean Before	No Tests	Mean Dur. 1	Dose of Hydral- azine
Began on Hydralazine	4	9	24.5 (17.3-33.5)	18	15.5 (11.2-23.2)	150-600
On Hydralazine for 1-3 Years	6			28	13.6 (5.5-18.7)	200-600
■ EDTA†	3	10	22.1	15	24.0 (12.0-36.0)	
On EDTA and hydral- azine	4			23	12.7 (4.4-18.8)	200-600
Normal	5	22	21.8			
Atherosclerosis	4	23	21.4			

Per 4 hours after 50 mg. orally of pyridoxal hydrochloride

† Calcium disodium ethylenediamine tetraacetate intravenously

The ranges for each group shown in italics are the mean excretion rates of each patient

the specificity of the hydralazines for a reaction not exhibited by other hydrazides and similar agents

The known actions of hydralazine are listed in Table XV. The actions of a large number of similar substances are shown in Table XIII as regards the two enzyme systems considered here.

Other Metal Finding Agents Thiocyanate ion is used in industry for making soluble salts of a number of metals. In man, according to Sollmann (173), it has been

used in the form of soluble salts of thiocyanate. Symptoms

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W EDTA†	3	10	22.1	15	24.0 (22.0-26.0)	
On EDTA and hydral- azine	4			23	12.7 (4.4-19.0)	200-600
Normal	3	22	21.8			
Atherosclerosis	4	22	27.4			

For 4 hours after 5 mg. orally 1 pyridoxal hydrochloride

† Calcium di-sodium ethylenediamine tetraacetate intravenously

The ranges for each group shown in italics are the mean excretion rates of each patient

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On EDTA†	3	10	22.1	15	24.0 (2.0-26.0)	
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Normal	5	22	21.8			
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TABLE XV—(continued)

Vascular Reactions in Animals	References
Dilates constricted vessels renal femoral coronary acts for many hours	(438)
Does not dilate dilated vessels further (as in spinal animal)	(438)
Abolishes constriction caused by Ba pitressin ephed rine ergotamine histamine Privine	(438)
Reactions in Man	
Lowering of plasma cholesterol	(180)
No lowering of blood pyruvate or total carbonyl	(168)
Apparent loss of Ti in urine	
Mild anemia	(168)
? Histamine release	(172)
Increases cardiac output tachycardia	(425)
Increases renal plasma flow	(426 427)

and side effects due to this ion are variable but resemble in some respects those induced by hydralazine because of the dissimilarity of the chemical structures of the two

TABLE XVI
SOLUBLE COMPLEXES OF THIOCYANATES IN WATER

Soluble	Partly Soluble	Insoluble
Mn	Pb	Cu
Fe	Hg	Ti ?
Co	Ag	Si
Zn		
Mo		
Ca		
Sr		
Ba		

Hodgman C. I. ed. *Handbook of Chemistry and Physics* 33rd Ed.
Cleveland Chemical Rubber Publishing Co. 1951

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Sodium azide which has a strong affinity for metals is a rather transient vasodilator, as is its relative choline azide producing sharp reductions in blood pressure. It is said to show differential actions in normotensive and hypertensive rats not depressing blood pressure in the former (175). We have been unable to confirm claims for chronic effects in man.

British Anti Lewisite (2,3-dimercaptopropanol BAL) is used clinically to remove trace metals from the body. Much is known of its actions (176, 177, 178) which do not include affinities for all metals. It is a disulfide chelating agent. In our hands it has proven effective in causing lowering of blood pressure in American hypertensive patients for periods of a few hours. On the other hand British patients have responded with a rise. It is prolongedly pressor in normotensive subjects (177) but was depressor in one American hypertensive patient in the hands of others (176). BAL has little clinical use at present in hypertension. In cadmium poisoning it will mobilize the metal but binding is weaker than is that of kidney for the metal is deposited and cadmium nephritis results (179). Many other heavy metals are mobilized and removed in the urine.

Ethylenediamine tetra acetate is a mild antihypertensive agent in man. Given intravenously as the disodium calcium complex it either lowers elevated blood pressure or reduces the patient's requirement for ganglionic blocking agents (180). Not a strong chelating agent for many metals, it has little clinical use at present. Prolonged oral use has led to no toxicity; intravenous use has produced signs of zinc deficiency (181) which resembles that of vitamin B₆.

Experimental Compounds In anaesthetized rats and other animals a number of compounds having the capacity for binding or chelating trace metals lower hypertensive

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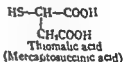
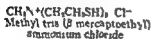
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both types of animals D Lowering of blood pressure in both types of rats and depression of the pressor action of norepinephrine E Lowering of the blood pressure of both normotensive and hypertensive rats without greater effect on the latter and without altering the pressor action of norepinephrine (Fig 11)

Mercaptan compounds which showed specific antihypertensive but not sympatholytic effects (Type A) in the rat were

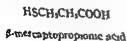


Procaine Salt of β mercapto-
propionic acid



1-ethyl 2 mercaptoimidazole

Compounds showing both antihypertensive and norepinephrine blockade (Type C) were



and to a less extent



both types of animals D Lowering of blood pressure in both types of rats and depression of the pressor action of norepinephrine E Lowering of the blood pressure of both normotensive and hypertensive rats without greater effect on the latter and without altering the pressor action of norepinephrine (Fig 11)

Mercaptan compounds which showed specific antihypertensive but not sympatholytic effects (Type A) in the rat were

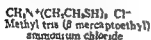


Thioglycolic acid



β mercaptoethylamine

Procaine Salt of β mercaptopropionic acid



Methyl tris (β mercaptoethyl) ammonium chloride



2 Mercaptoethanol



Ethyl β mercaptopropionate



Thiomalic acid

(Mercaptosuccinic acid)



1-ethyl 2 mercaptimidazole

Compounds showing both antihypertensive and norepinephrine blockade (Type C) were



β -mercaptopropionic acid



Reduced glutathione

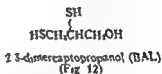
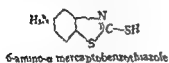


and to a less extent

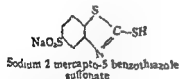


mercaptopyruvic acid
(ammonium salt)

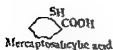
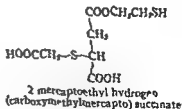
Certain mercaptans were depressor in both types of animals (Type E) although the last two showed significant differential activities



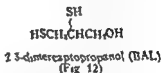
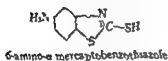
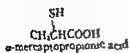
Only four mercaptans were sympatholytic (Type B) without depressor effects the last to a lesser degree



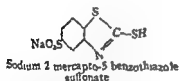
Five were inactive or pressor the last having a short lived differential action



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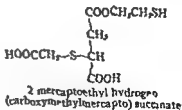
Only four mercaptans were sympatholytic (Type B) without depressor effects the last to a lesser degree



Five were inactive or pressor the last having a short lived differential action



Cysteine



A group of sulfur-containing compounds were similarly divided Type A activity was demonstrated by

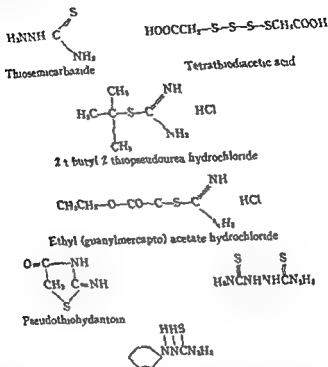


FIG 12 A. Transient effect of 23 dimercaptopropanol (BAL) on systolic pressure of renal hypertensive rat. Blood pressure was measured by the foot cuff method using a photoelectric cell. The open circles are measurements made 2, 3 and 4 hours after the injection; the closed circles 24 hours later. Note increasing tolerance.

B. Effect of BAL on blood pressure of a 59-year-old patient receiving hydralazine (5968) and hexamethonium chloride (Ca) in too low doses to produce normotension. Doses are indicated at the top. BAL, 50 mg every four hours intramuscularly was given for four doses. At the bottom urinary excretion of hexamethonium ion and hydralazine are shown. The solid black areas represent free urinary hydralazine; the open areas that bound to sulfhydryl. All excreted hydralazine was bound after BAL was given. (From Perry H. M., Jr., Schroeder H. A. and Morrow J. D. *Am J Med Sci* 228:405, 1954.)

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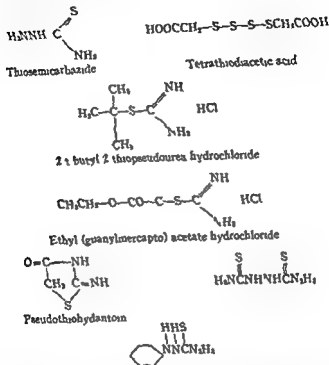
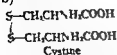


FIG 12 A. Transient effect of 2:3 dimercaptopropanol (BAL) on systolic pressure of renal hypertensive rat. Blood pressure was measured by the foot cuff method using a photoelectric cell. The open circles are measurements made 2, 3, and 4 hours after the injection; the closed circles 24 hours later. Note increasing tolerance.

B. Effect of BAL on blood pressure of a 59-year-old patient receiving hydralazine (5968) and hexamethonium chloride (C_6) in too low doses to produce normotension. Doses are indicated at the top. BAL, 50 mg every four hours intramuscularly was given for four doses. At the bottom urinary excretion of hexamethonium ion and hydralazine are shown. The solid black areas represent free urinary hydralazine; the open areas that bound to sulfhydryl. All excreted hydralazine was bound after BAL was given. (From Perry H. M. Jr, Schroeder H. A. and Morrow J. D. *Am J Med Sci* 228:405, 1954)

There was no activity exhibited by oxidized glutathione nor by

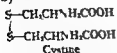


One compound of interest contained three ethyl mercaptans on a quaternary ammonium nitrogen it was made on the possibility that ganglionic blockade as well as mercaptan effect might result. However it acutely raised the mean diastolic pressures of normal and hypertensive rats 36 and 15 mm Hg respectively producing the usual differential mercaptan effect of a depression of 6 and 32 mm respectively at the end of 2 hours. Another of special interest had the basic structure of hexamethonium ion with an ethyl thiopseudourea group on each quaternary nitrogen. Although listed as Type E it depressed the mean diastolic pressure of 5 normal rats 36 mm. Hg and that of 5 hypertensive rats 86 mm in doses of 10 to 15 mg. Possibly ganglionic blockade was combined with another action on the renal pressor mechanism.

Examination of the structures reveals that antihypertensive or depressor activity was confined to those aliphatic compounds having a terminal sulfhydryl group or SCNH in the molecule unencumbered by a heavy salt. Aromatic compounds containing SCN were likewise active. Such compounds usually bind metals, sulfur nitrogen binding being strongest with Cu, Ni, Ag, Cd and contiguous heavier elements in the periodic table. These results suggest that possibly some copper enzyme was altered or inactivated causing the pharmacological activities of the compounds (182).

If this surmise be true the next step was obviously to test known chelating agents in the same system preferably those not metabolized. If they were active obviously a metalloenzyme was altered.

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In order further to control the studies various pyridoxylidene metal amino complexes were subjected to the same test. Selective Type A effects were observed with the copper tyrosine nickel arginine aluminum phenylalanine and possibly the cobalt phenylalanine complexes. No ef

DIVALENT METAL DISODIUM ETHYLENE DIAMINE TETRA ACETATE

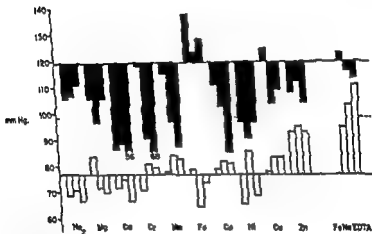


FIG 19 The effects of various metal complexes of ethylene-diamine on the blood pressure of hypertensive and normotensive rats. The solid black bar represents the change 20 to 30 minutes after one intravenous injection of 11 mg. the second and third changes a like interval after subsequent injections. Mean changes are shown each group representing at least 3 and usually 4 or more rats. All complexes were dihydrogen metal except for ferric as shown on the right. Note the comparable differences in hypertensive (mean diastolic pressure 119 mm. Hg) and normotensive animals (mean diastolic pressure 77 mm. Hg).

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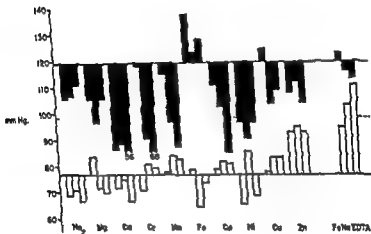


Fig 13 The effects of *various metal complexes* of ethylene-diamine of hypertensive *tized rats*. The *first solid black metal complex* represents the change 20 to 30 minutes after one intravenous injection of 5 mg the second and third changes a like interval after subsequent injections. Mean changes are shown each group representing at least 3 and usually 4 or more rats. All complexes were dihydrogen metal except for ferric as shown on the right. Note the comparable differences in hypertensive (mean diastolic pressure 119 mm. Hg) and normotensive animals (mean diastolic pressure 77 mm. Hg).

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Comment This common denominator of the antihyper

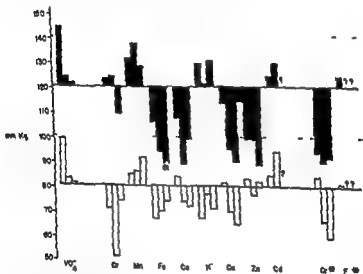


FIG 14 The effects of a series of metal ions on the diastolic pressures of groups of hypertensive and normotensive (mean similarly treated). Calcium salts were indicated as well as. Note the differences between the ions and their control

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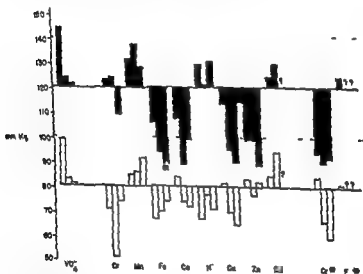


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lowing chapters

THE EFFECT OF ANTIHYPERTENSIVE AGENTS ON NEPHROGENIC EFFECTOR SUBSTANCES

A method for screening antihypertensive agents involves the isolated rabbit aortic strip a spirally cut piece of smooth muscle which contracts when pressor substances are applied (120). Substances acting mainly on norepinephrine and other primary amines acting on more complex pressor substances and showing general inhibition of all types can be evaluated. While many agents tested cannot be applied to man their activities can be evaluated readily on isolated muscle and in the hypertensive animal. A substance which is nontoxic inhibits pherentasin and lowers the blood pressure of hypertensive rats while not affecting normotension is obviously of therapeutic interest.

Pherentasin. Using the isolated rabbit aorta suspended in oxygenated Ringer's solution a number of these substances have been tested for their activities against pherentasin. The relative degrees of inhibition are indicated in Table VII. All of the metal binding agents are inhibitory. On the possibility that pherentasin may be an adrenergic agent a number of sympatholytic substances

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APRESOLINE BLOCKADE OF PHERENTASIN

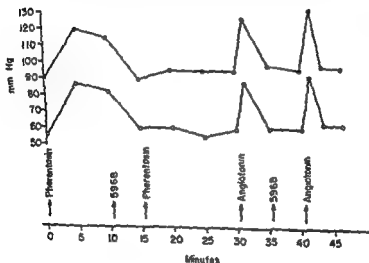


FIG 16
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response however 10 units of pherentasin caused little re
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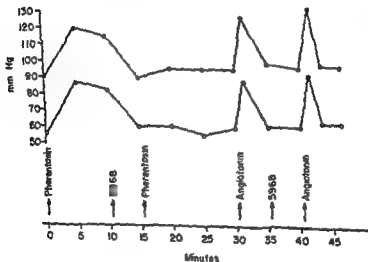


FIG 16
of ph
into a
At 10
intrav
subsec

Injection of 20 units of pherentasin caused little response however 10 unit of angiotonin was pressor At 35 minutes 50 mg of 5968 was injected the response to another unit of angiotonin 5 minutes later was not inhibited (From Perry H M Jr and Schroeder H A. *Am J M Sc* 228 596 1954)

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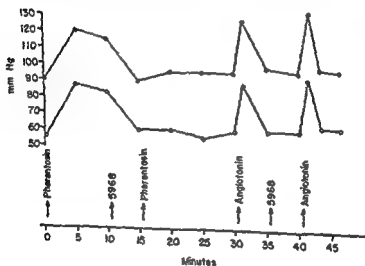


FIG 16 At 0 minutes after a control period of 20 minutes 10 unit of pherentasin previously found active was injected intravenously into a rat with the response of systolic and diastolic pressure shown. At 10 minutes 10 mg of hydralazine (apresoline 5968) was injected intravenously resulting in an immediate fall of blood pressure. A subsequent injection of 20 units of pherentasin caused little response however 10 unit of angiotonin was pressor. At 30 minutes 50 mg of 5968 was injected the response to another unit of angiotonin 5 minutes later was not inhibited. (From Perry H M Jr and Schroeder H A *Am J M Sc* 228 396 1954)

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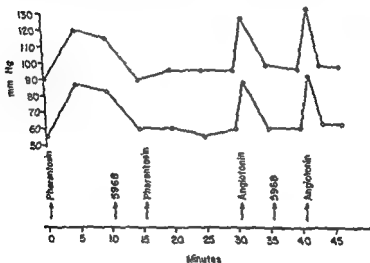


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ever acute arthritis and prostration have occurred within a few hours of giving the drug or its analogues (185-189) both to patients recovering from hydralazine disease and to others never receiving the drug before. We have seen showers of L-E cells appear in one recovered person who had taken no drug for 2 years and was given small doses. In several other individuals reduction of doses has resulted in reversal of symptoms but not of all laboratory abnormalities. If the L-E phenomenon is one of hypersensitivity which is not known this explanation for the disease is tenable. The question is open but we suspect that its answer will be fruitful of information on hypersensitivity collagen disease and hypertension.

We do not know which substance is removed from the body by hydralazine or which enzyme system or group of systems is inactivated. The ability to produce this syndrome in man by a drug however suggests that lupus erythematosus itself is an enzymatic disturbance which might be affected by replacement therapy. A suggestion of what has been removed in the way of metals may be obtained from trace metal analysis of human urine when hydralazine was given and from cases of known hydralazine disease and known lupus erythematosus (Table XX). The abnormal urines are somewhat low in manganese somewhat high in tin and zinc. While these findings may not be pertinent to pathogenesis they deserve study. Blood copper levels were not reduced in this syndrome.

Of the other known functions of hydralazine carbonyl binding is the most logical to explain the toxicity. It is difficult however to conceive of carbonyl binding as leading to depletion. There was no diminution in total carbonyl or pyruvate in blood of patients treated with hydralazine. Its other function removal of sulfhydryl is also a possible but not probable cause of hydralazine

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disease. Its known antihistaminase activity and the relation of histamine to hypersensitivity is another possible explanation as is its affinity for pyridoxal.

Lest the reader refrain from using this potent agent when it is needed for the prolongation of life we can say that hydralazine disease occurs in less than 10 per cent of patients and then only when relatively large doses are given that it is readily detectable easily reversible and does no permanent harm if the drug is discontinued in time. There has been no mortality except in unwatched patients and the drug on the whole is hardly more toxic than many in continuous use for the control of chronic diseases. The method of use is discussed in Chapter VIII.

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THEORY OF HABITUAL REPETITIVE STIMULI

One idea is that the trigger mechanism for emotional discharge to vasospasm becomes more sensitive as the years pass, lesser and lesser stimuli setting off the response. In other words, an habitual pattern of reaction is set up which becomes more and more active and eventually leads to organic renal vascular disease, thereby causing organic renal ischemia. This explanation begs the question and is inconsistent with the fact that demonstrable renal vascular disease may be absent in sustained hypertension.

THEORY OF DEPLETION OF VASCULAR SUBSTANCES

Another theory is concerned with the depletion of substances or the wearing out of the mechanisms which cause reversal of vasospasm, i.e. the relaxation of smooth muscle. In other words, repetitive stresses accelerate the aging process in smooth muscle, making it more reactive. There is no evidence for this theory, although as Szent-Gyorgyi has pointed out (190), contraction of muscle involves loss of potential energy, relaxation a build up of energy (phosphate) in the contractile elements. Therefore, slight loss of some substance promoting the restoration of the energy for relaxation may occur with time, or possibly inhibition of the mechanisms of energy storage by accumulation of another substance. In that event, permanent vasospasm

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may be no vascular lesions no organic renal disease no organic renal ischemia but functional changes are found which are obviously dependent upon circulating vasoconstrictor substances provoking spasm. In the dog spasm is even present distal to renal arterial constriction (10). What is the reason?

To find the answer we must delve deeper into those mechanisms affected by ischemia in order to think of similar ones altered in the functional state. Something has happened to the kidneys of patients with sustained functional hypertension which may be similarly affected in organic renal ischemia. We look to altered enzymatic mechanisms to supply us with a common denominator. Because ischemia is related to oxygen tension and oxygen consumption oxidative mechanisms are the first to be considered. Is it possible therefore that some renal oxidative enzyme in man is reduced in function by both organic ischemia and an exogenous accumulating substance? If this were so a population might be exposed uniformly to this substance but only certain members predisposed to hypertension i.e. those who react to stress by vasospasm might develop permanent disease.

Pickering put forth this same idea that a whole population was contaminated but only certain persons developed the disease (Chapter II). This theory is the only one consistent with the known facts and which explains the virtual absence of the disease in many areas of the world. For it is likely that a proportion of all human beings react to stress by neurogenic discharges through the sympathetic nervous system.

There are two possibilities intimately related which should be explored in order to discover this basic disturbance. Both could explain this most important factor. One involves vitamin B₆ one trace metals.

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pregnant women appear to be somewhat deficient the growing fetus apparently removing the vitamin from the mother without causing skin lesions (203-205) Army combat rations were found deficient for monkeys and rats (206-207) and a brand of infant food was found deficient, causing convulsions (208, 209)

✓ As we have said there is obviously no generalized deficiency state which can be recognized in the American adult population. Marginal intakes however are possible, especially during seasons of the year when the diet is composed largely of processed foods. Converting the values in foods described in the literature to include a daily diet we have found that the intake is barely adequate (202). About 0.2 mg per 100 Gm of food is necessary to promote the growth of rats. Not many foods contain this much when cooked and it was difficult to calculate a 20 mg intake in a sample hospital diet (202).

Why do not pronounced deficiency symptoms appear? Apparently this coenzyme has an affinity for systems where it is most needed for life and less for health. Its distribution in organs shows wide variations (201). Perhaps renal deficiency can exist without deficiencies elsewhere, perhaps overloading of one vitamin B₁₂ enzyme system by metabolic products can produce a state of local deficiency without it being manifest in other systems. The need for a coenzyme varies as the load placed upon the enzyme system as is so well known in the case of vitamin B₁₂ or niacin. A third possibility is that specific antagonists accumulate with age.

Trace Metal Imbalance The second theory concerns metalloenzymes. There are many in the kidney. If deficiency of a metal were produced that enzyme would be

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come inactive until the metal were replaced. There is no evidence at the present time that specific metal deficiencies exist in man with the possible exception of zinc in under nutrition. On the contrary there are many trace metals in American tissues which perhaps are not only unnecessary but undesirable. The kidney is notable in this respect (Chapter VI).

(Because an undesirable metal can replace an essential one in an enzyme system and inactivate it *in vitro*, it is probable that such a consequence can occur *in vivo*.) In order to determine where to look we must examine the essential and the presumably abnormal trace metals in American human adult tissues and urine (Table XVI) compare them with metals found in infants to discover which accumulate with age and also compare the tissue content of people from areas not exposed to hypertension. This subject will be discussed in Chapter VI but examples can be considered here.

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An examination of the inhibitory effects of a number of trace metals upon DOPA decarboxylase and monamine oxidase revealed the following. Some inhibition was exhibited by all in high concentrations but at low (0.1 millimolar) only cadmium and mercury significantly inhibited enzymatic activity of DOPA decarboxylase both inhibited monamine oxidase to less extent (Table XXIII). Both are nephrotoxic and will displace zinc (p. 146).

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tion of those abnormal trace metals to which civilized man is exposed. Cardiovascular diseases associated with aging therefore may be influenced by accumulation of trace metals in kidney, liver, blood vessels, adrenal or brain.

In Table XXII are shown evidences of accumulation of various trace metals or lack of it in American kidneys with age. Although the numbers in each decade are small, the trends are definite for nickel, titanium and cadmium, not so for tin. Zinc is accumulated in proportion to cadmium. One of these metals could be the culprit, although we suspect cadmium because of its prevalence (see p. 146).

Other oxidative metalloenzymes in kidney (or elsewhere) might be affected by abnormal exogenous trace metals. Two pertaining to the problem of hypertension are listed in Table XXIII. (Any enzyme containing free sulphhydryl groups can be inactivated by metal binding thereon; thus metalloenzymes are not essential for inactivation by metals.) Direct evidence for their participation is lacking, but they are shown to call attention to their role in nitrogen metabolism, direct or indirect, and to their metalloenzyme natures. Vanadium and cadmium have striking actions.

Theory of Electrolyte Imbalance. Small elevations in the serum sodium of hypertensive patients have been reported from time to time (210-211). Their significance is unclear. The hypertensive kidney is a salt-losing kidney; no functional or morphological alterations in adrenal cortex have been demonstrated in the usual case. There is evidence, however, that the sodium content of arterial walls may be increased, causing enough swelling to increase peripheral resistance (212). There is also evidence that the sodium in the body affects vascular irritability in that the peripheral vessels become less sensitive in sodium depletion and more sensitive in sodium repletion and the administration of desoxycorticosterone acc-

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tate. What change affecting sodium intake, loss or shift occurs in hypertension is not known. There is no correlation with salt intake in man although moderately hypertensive rats choose to eat more. The alteration must be a systemic one and may involve potassium and mag-

Obstruction

In view of the above discussion it is highly possible that enzymatic alterations secondary to organic ischemia and those caused by one or more of the aforementioned factors may be similar. If so, partial obstruction of a renal artery by atherosclerotic plaques could provide the necessary mechanism for permanent hypertension just as well as could intrarenal enzymatic changes from trace metals or coenzyme deficiency. Such obstructive lesions exist and may be more common than realized (145). One can imagine a hypothetical case: a man with the ability to react to stress by vasospasm passes through his first five decades only with tachycardia or transient hypertension under the stimulus of an examination. In his fifth decade in our civilization he begins to develop overt atherosclerosis; plaques of which are deposited by chance or by dynamic design at the mouths of his renal arteries. He then develops hypertension caused by some organic renal ischemia and some neurogenic vasospasm. As the hypertension increases the rate of development of atherosclerosis these plaques may become larger leading to further renal ischemia and hypertension but without much intrarenal arterial sclerosis. He dies in his sixth or seventh decade usually of an atherosclerotic complication. This sequence of events may be very common and does not necessitate trace metal imbalance or other enzymatic disturbance unless a common disturbance influences both hypertension and atherosclerosis (Chapter VII). Further

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Similarly the tubular part of the nephron may be unable to distinguish the difference between organic arterial and arteriolar narrowing from these causes or from intra renal arterial obstruction by scars (pyelonephritis) and glomerular obstruction (nephritis and glomerulosclerosis). The locus of the mechanism reacting to renal ischemia may be postglomerular (tubular) or it may be in the juxta glomerular apparatus which lies around the afferent arteriole. In the latter case chronic glomerulonephritis might not be expected to cause hypertension until fairly widespread renal degeneration had occurred. This may be the usual situation.

Comment One can only guess at which factor operates in a given hypertensive patient. There may be several others not mentioned. The theory of vicious cycles or cybernetics is quite prominent in much of what has been said as it is in many pathologic states and normal metabolic pathways (which are far from vicious until disturbed). This mechanism which transforms intermittent neurogenic vasospasm into permanent nephrogenic and neurogenic hypertension, is the 'kill-r'. Therefore it becomes of foremost importance to understand it for treatment. If:

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TABLE XIV
VARIOUS EFFECTS OF PYRIDOXINE IN MAN WITH ESPECIAL REFERENCE TO ANTAGONISM TO METAL-BINDING AGENTS

<i>Clinical Finding</i>	<i>Induced by Metal binding Drug</i>	<i>Relieved by Vitamin B₆</i>	<i>No Reports</i>	<i>Remarks</i>
Convulsions	Isoniazid	Yes	1	
Convulsions	Semicarbazide	Yes	1	
Peripheral Neuritis	Isoniazid	Partly	1	Local disorder
Leukopenia and agranulocytosis	Thioureacl	Yes	5	
	Sulfonamides	Yes	2	
Peripheral Neuritis	Arsenic	Yes	1	
Cheilosis Chemoosis etc	EDTA	No	1	Zinc deficiency
Same	Desoxy pyridoxine	Yes	1	
Same	Spontaneous	Yes	8	
Seborrheic Dermatitis	Desoxypyridoxine	Yes	2	Applied locally
Same	Spontaneous	Yes	4	

Vitamin B₆ Selected Annotated Bibliography 1954 Merck & Co

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	Thioracil	Yes	5	
Leukopenia and agranulocytosis	Sulfonamides	Yes	2	
	Arsenic	Yes	1	
Peripheral Neuritis				Zinc deficiency
Cheilosis	EDTA	No	1	
Same	Deoxy pyridoxine	Yes	2	
Same	Spontaneous	Yes	8	
Seborrheic Dermatitis	Deoxypyridoxine	Yes	2	
Same	Spontaneous	Yes	4	Applied locally

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mechanisms are unknown but the clinical and laboratory evidence that adrenal steroids cause hypertension in certain cases is clear. The reader should remember, however, that there is no evidence that the adrenal cortex is overactive in most cases of neurogenic or nephrogenic hypertension but that isolated instances in which it plays a definite and perhaps primary role are known.

Experimental Steroid Hypertension For many years it has been recognized that desoxycorticosterone (DOCA) a salt retaining hormone will cause hypertension in rats when added salt is given (216-217). Likewise a syndrome similar to toxemia of pregnancy can also be produced relieved or prevented by hydralazine (218). Feeding of salt alone in excessive quantities can produce rat hypertension (219); vascular lesions result. The amount of steroid and the amount of salt necessary to produce this disorder are far beyond physiologic limits. DOCA is pressor in renal hypertensive dogs (220) and hypertensive patients (221). Salt restriction apparently induces adrenal cortical hyperactivity (222).

Effect of Experimental Nephrogenic Hypertension on Adrenals Adrenal hypertrophy accompanies experimental nephrogenic hypertension (223). Furthermore rats with moderate hypertension voluntarily drink more saline than do normals or their paired severely hypertensive mates (224). This increased requirement for salt may be a reflection of the salt losing tendencies of ischemic kidneys already discussed in Chapter IV.

Relation of Adrenal Cortex to Medulla It may not be a coincidence that the adrenal medulla concerned with the release of epinephrine and the cortex concerned with sugar, salt and sex, are enclosed in the same gland. There is an intimate relationship between the two hormones acting on vascular smooth muscle. There may be a further

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These interactions between nerve transmission salt vasoconstrictor substances and steroids can explain some of the clinical findings which appear on the surface to be inexplicable Normal vasomotor tone normal discharges of sympathetic fibres normal amounts of norepinephrine can produce generalized vasospasm when the vascular smooth muscle becomes hypersensitive through salt and steroids Removal of salt or steroids may restore sensitivity to normal Excessive vasomotor tone excessive discharges of sympathetic fibres excessive amounts of norepinephrine formed at nerve endings can produce a much greater degree of generalized vasospasm when the vascular smooth muscle becomes hypersensitive Removal of salt or steroids restores sensitivity to normal but does no more than partly reduce the vasospasm to a lesser level to achieve strict normality requires additional restoration of sympathetic activity to normal When the vasospasm is in part caused by circulating humoral pressor substances restoration to a normal state is impossible unless these substances are inactivated

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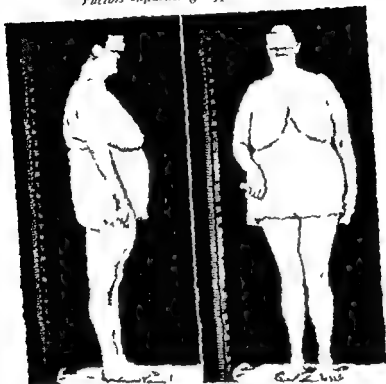


FIG 1: Central obesity, menstrual irregularities, low sweat salt (< 20 mEq/L) and hypertension. Rapid weight gain, mild hirsutism, easy bruisability and moderate diabetes were also present. This complex has been named the "endocrine hypertensive syndrome" - for want of a more definitive word. The blood pressure was highly responsive to salt restriction (3-3c).

They may be recognized by the presence of central obesity and hypertension. In women, menstrual irregularities are common (Fig. 17). The condition has been seen in families (3). Presumably their hypertension is influenced by an overproduction of aldosterone or other salt retaining hormones which decreases the sodium in sweat to low levels. We must hypothesize the chain of events as the

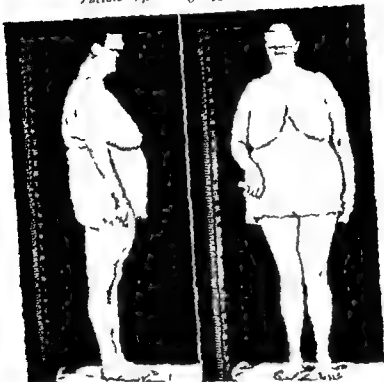


FIG 1. Central obesity, menstrual irregularities, low sodium salt (< 40 mEq/L) and hypertension. Rapid weight gain, mild hirsutism, easy bruisability and moderate diabetes were also present. This complex has been named the endocrine hypertensive syndrome for want of a more definitive word. The blood pressure was highly responsive to salt restriction (3, 3c).

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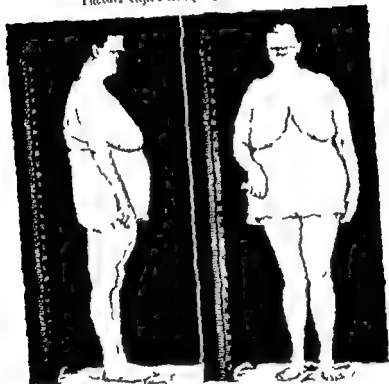


FIG 17 Central obesity, menstrual irregularities, low sweat salts (< 20 mEq/l) and hypertension. Rapid weight gain, mild hirsutism, erythema, and moderate diabetes were also present. This complex has been named the "endocrine hypertensive syndrome" for want of a more definitive word. The blood pressure was highly responsive to salt restriction (3-3c).

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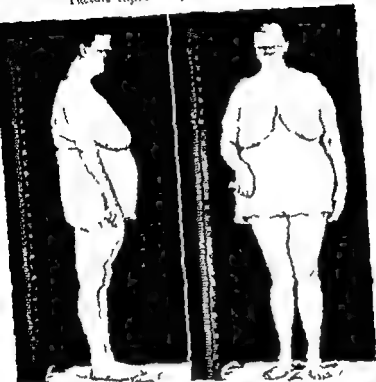


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CLINICAL IMPLICATIONS

Obviously patients with hypertension influenced by adrenal cortical overactivity should respond to restriction of salt by a lowered blood pressure. They do. The fact that severe salt restriction causes a fall in blood pressure in these cases does not mean that all human hypertension is dependant upon steroids and salt. On the contrary these cases are in a minority. The reader must remember the simple fact that dietary salt restriction of severe degree causes overactivity of the adrenal cortex and that the usual hypertensive kidney is a salt losing kidney to an extent dependant upon the degree of renal damage or renal ischemia.

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Chapter VI

TRACE METALS AND CARDIOVASCULAR DISEASE

INTRODUCTION

BECAUSE of the strong suggestion that trace metal imbalances may be involved in some of the chronic diseases to which the people of Western Civilization are exposed a chapter on this subject is in order. To be considered are the relations of metalloenzymes to the problem, the concentrations of essential trace metals in human tissues, the presence and amount of abnormal metals and from whence they may come, and the possibility of their interference with metalloenzymes to such an extent that they cause chronic diseases. Because this subject represents a new frontier in Medicine, vast gaps in knowledge exist but the pattern is clearing.

By trace metals we will consider only those present in small or relatively minute amounts and not discuss the bulk metals sodium, potassium, magnesium and calcium, nor iron which has an intermediary position between ubiquitous elements and trace metals. All bulk metals probably take part in enzymatic reactions or in exchange mechanisms; trace metals are often confined to more specialized systems. If interference with one of the bulk metals occurred in the body, profound toxicity would result. For example, should all magnesium enzymes be inhibited, intermediary metabolism would cease, if calcium were displaced, muscular relaxation would cease. Partial

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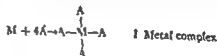
have a coordination number of 4 or 6 an index of the number of donors of the chelate with which the metal will combine. Thus magnesium aluminum vanadium chromic ion manganous and manganic ferrous and ferric, cobaltous and cobaltic nickelous and nickelic tin and lead have coordination numbers of 6 while zinc cupric cadmium mercury silver gold have one of 4 and molybdenum of 8. Those of titanium and scandium have not been determined (233). Some functional groupings which bind metals are carboxyl hydroxyl carbonyl amino (primary secondary tertiary cyclic tertiary) sulphhydryl thioether sulfonate and phosphonate (232).

Principles of Chelation The general rules regulating the stability of metal chelates according to Bailar (234) are as follows:

1 Ring structures involving metals and organic com-

2. A = 5 membered rings in its presence are the most stable

3 Fused rings that is configurations in which two or more rings have a common side have a greatly increased



where M represents a metal ion, A represents a complexing agent and A—A represents a chelating agent.

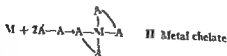
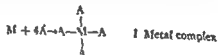
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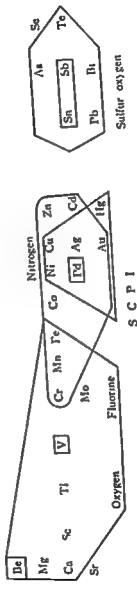
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TABLE XV
AFFINITIES OF VARIOUS COMMON TRACE METALS FOR CHELATION BY DIFFERENT ACTIVE GROUPS



After Bailar (234)

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Certain metalloenzyme systems need organic coenzymes (or vitamins) for activity One possible example is pyridoxal phosphate which according to Snell requires a metal for the coenzyme to become activated (215) While the metal is not known model systems constructed without the apoenzyme suggest that either copper iron or aluminum could be the essential one (237) It is apparently so firmly bound that most metal binding agents will not remove it Other well known examples are riboflavin where flavin adenine nucleotide is intimately bound with the oxidation and reduction of iron and the copper flavinoid in acyl Coenzyme A-dehydrogenase Other members of the vitamin B group in some cases may require metals for activity magnesium with thiamine and molybdenum with flavin adenine nucleotide are examples

In general the active essential metals are divalent and in the first transitional group of the periodic table Copper is essential for phenolic and catecholic oxidation and for fat metabolism Manganese is required for peptide splitting and for carboxylation In view of the high concentrations of zinc in tissues and the very few zinc enzymes found carbonic anhydrase being the most prevalent it is possible that others exist The metallo-porphyrins are good examples of chelates heme the prosthetic group of hemoglobin has iron chelated to four methyl pyrrole rings the iron porphyrins of the cytochromes and myoglobin vitamin B¹² has cobalt chelated in a porphyrin structure and the porphyrin of chlorophyll chelates magnesium There are several metalloproteins known ceruloplasmin and hemocuprein contain copper mercaptalbumins ap-

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TABLE XVIII—(continued)

	Mg ⁺⁺ Ca ⁺⁺	Mg ⁺⁺ Mg ⁺⁺ (+K ⁺)	Zn + Co ⁺⁺ Ni ⁺⁺ Cd +		Pho phenol pyruvate to ADP Inhibited by Mg ⁺⁺
Alkaline ATPase Hexosediphosphate Transphorylase Flavokinase Actomyosin Arginine ATP transphorylase I ho phoglucomutase Ilevokinase I nolase	Mg ⁺⁺ Ca ⁺⁺	Mg ⁺⁺ Mg ⁺⁺ (+K ⁺)		Riboflavin	
<i>Dehydrogenases</i> I ho phogluconic acid Isocitric Alcohol	Mg ⁺⁺ Mn ⁺⁺ Zn ⁺⁺	Mg ⁺⁺ or Mn ⁺⁺	Zn ⁺⁺ Mn ⁺⁺		
Oxidases Xanthine Aldehyde Monamine	Mn ⁺⁺ Mn ⁺⁺ V ^{IV}			FAD FAD	0.03% Mo Only activator Metal not known
Histaminase Decarboxylases 5 hydroxytryptophan DOPA Histidine Oxalacetate	? Zn ⁺⁺ Zn ⁺⁺ ? Mn ⁺⁺		Mn ⁺⁺ Mg ⁺⁺ Co ⁺⁺	Pyridoxal PO ₄ ? Pyridoxal PO ₄ Pyridoxal PO ₄ Pyridoxal PO ₄	Metal inferred† Metal not known
<i>Others</i> Transaminase Urease	? Zn ⁺⁺			Pyridoxal PO ₄	Metal not known

† See Table VIII p 176 and p 154

have an affinity for bone both strontium and beryllium can cause rickets and beryllium displaces magnesium on phosphatases inactivating them. Therefore all but magnesium are concentrated by one tissue. Similarly two anionic and all cationic elements in group VII have been shown to be concentrated by the thyroid: iodine, astatine, manganese, technetium and rhenium; those of the halide sub-group quite specifically (239-242). Likewise in group V A bismuth, antimony and arsenic are believed to displace phosphorus in phosphates. Gold, silver and copper of group I B have strong affinities for each other as does cadmium for zinc in group II B; complete separation of the two from ores is difficult and often too expensive for commercial purposes. Cadmium displaces zinc on human mercaptalbumin while lead does not, presumably because the former two ions bind the same molecular group (the 16 imidazole groups) while the latter binds at a different site. Cadmium therefore has a higher affinity than zinc for this protein. Similarly cupric ion is displaced from the sulphhydryl groups of bovine serum albumin by metals in the following order of affinity: $\text{Hg}^{++} > \text{Pb}^{++} > \text{Cd}^{++} > \text{Zn}^{++}$ (243). Among the anions, fluorine, chlorine, bromine and iodine are biologically interrelated while selenium and tellurium of group VII A will displace sulfur in hair and nails, possibly in sulphhydryl groups. In group I A, radio-rubidium is used to measure potassium space (244).

Metalloenzyme Inhibitions. In spite of these obvious relationships in biological material, metalloenzyme competition by an extraneous metal has not been systematically studied. In Table XXVIII are shown examples of cases where an extraneous metal apparently displaces an active metallic prosthetic group. The list may be far from complete. At least two types of enzyme inhibition can occur

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One is when a heavy metal combines with sulphydryl groups to inactivate the enzyme. Mercury, copper and silver will inactivate many enzymes which do not contain a metal (245). Presumably, the toxic effects of many heavy metals are due to this type of reaction. The second is when the essential metal is displaced by another, often of the same periodic group. Lerner has offered good examples of both types of reactions in respect to tyrosinase, essential for formation of melanin (246). Metals which compete with copper: Increased melanin pigmentation is frequently observed when heavy metals such as arsenic, bismuth, iron, gold, silver and mercury are deposited in the skin. Patients with hemochromatosis have relatively large amounts of iron and copper deposited in the skin. The most plausible explanation for these findings is that metals bind epidermal sulphydryl groups and thereby release inhibition of tyrosinase. The increased tyrosinase activity results in increased melanin formation. However, if sufficient quantities of the metals mercury, silver or gold are present, they can replace the copper of tyrosinase to produce an inactive enzyme with resultant depigmentation. It is possible that the slight decrease in skin color produced by ammoniated mercury freckle creams is achieved in this manner. Six copper-binding agents have caused depigmentation *in vivo* (247); most of them anti-thyroid drugs.

Essential metals such as copper, manganese, cobalt and zinc can interact to inhibit the metalloenzymes of each. Excess enzymatic activity by a presumably abnormal metal can also occur. For example, chromium causes increased synthesis of cholesterol and fatty acids by rat liver (248); cadmium and cobalt enhance bacterial oxalacetic carboxylase, a manganous enzyme; vanadyl ion enhances monamine oxidase (Table XXIII). Thus, both stimulation and depression by abnormal metal are possible.

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Each chelating compound differs widely in its affinity for different metals. In Table XXIX are shown the stability constants of a number of common oxygen and nitrogen chelators with divalent metals of the first transitional group and with cadmium. Ten of these compounds are present in biological fluids. In general an increase in tightness of structure is proportional to atomic number reaching a peak at copper (or nickel) and decreasing thereafter. This fundamental property of most chelating agents must be in mind whenever they are used. In effect this property means that a free ion having a higher stability constant with the chelator will displace a chelated metal with a lower constant. When the active groups are sulfur and other chelators the pattern of metallic affinity is different (Table XXV).

Metal Binding. Simple metal binding is dependent either upon the tightness of the bond, the lack of dissociation of the dissolved salt, or upon the insolubility of the complex. Thus complexes may be formed between metal and ammonia, metal and sulfhydryl, metal and cyanide, or metal and hydroxide. The stability constants for transitional metal complexes in solution are usually lower than for chelates, although mercury has a fairly high affinity for CN, NH₃, OH, and pyridine. The common law relating the stabilities of chelates of the first transitional group and atomic numbers appears to operate in the case of simple complexes of OH, CN, NH₃, and pyridine.

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transition groups. Numerous derivatives of salicylic acid containing the o-carboxyl hydroxyl group are about as effective as salicylic acid although they differ in dosage required and side effects. It might be anticipated that physiologically cortisone would have some resemblance to salicylates as has been demonstrated experimentally. Terramycin and aureomycin reverse the Be inhibition of alkaline phosphatase through the formation of a complex ion with Be. He lists as examples salicylic acid, adrenalin, terramycin, aureomycin, a thiosemicarbazone and cortisone. Penicillin forms insoluble salts with heavy metals.

Many chelating agents are fungicidal, antiseptic or bactericidal (233). Thirteen of nineteen common organic chelators of one or more transitional metals are listed by Martell and Calvin as effective against growth of *B. subtilis* with seven against growth of *E. Coli*. Likewise, 8-hydroxy quinoline of seven quinolines and 26 substituted quinolines of 35 are effective against the growth of *Clostridium welchii*, most of which inhibit *Streptococcus hemolyticus*, *Staphylococcus aureus* and *B. Coli*, less so *Proteus* and *Pseudomonas pyocyaneus*. Zinc and manganese appear to be bound although the other essential metals, iron and cobalt, may be involved. Apparently copper is not for copper reagents in general are inert. Few are effective against *pyocyaneus*, an organism resistant to most antibiotics. The fungicidal properties of the oxines, so widely used in industry, is believed to be the result of their chelation with zinc or iron.

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not metabolized (249) and apparently enters cells (250) it provides a means for removing soluble ions from the body in the order of their stability constants. If an abnormal trace metal is to be removed normal ones will accompany it according to the relative amounts and stability constants of each. Thus EDTA is not specific for lead for example a current popular use but will remove other ions with a higher constant such as copper and nickel and especially ferric iron. EDTA will be inactive however if the metals in the body are more tightly bound or chelated to protein than to the drug. This relative chelating capacity of a sequestering agent and a metal in the body follows certain definite laws and explains the ineffectiveness of EDTA for removing most metals.

An example of the effects of EDTA given intravenously to two patients is shown in Table XXX. Zinc was removed in sizeable quantities other metals less so or not at all. The high excretion of zinc in the patient with the nephrotic syndrome found before the drug was given is probably explained by the excessive proteinuria which carries combined zinc. There was no mobilization of lead while

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- 1 The stability constants ($\log K_s$) for common but important loosely bound metals is low ($Ba\ Sr\ Ca\ Mg = 7.76-10.96$)
- 2 The constants for more tightly bound metals is moderate ($Mn\ Fe^{++}\ Co\ Cu\ Zn = 14.04-18.8$)
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eight metals almost certainly present in a strongly bound form in their tissues did not change

BAL (2,3-dimercaptopropanol) a straight chain dithiol binds the following heavy metals in a chelate zinc chromium cadmium nickel, lead, antimony, arsenic, bismuth copper, mercury, gold (251) Substitution complexes on the sulphydryls are formed In the case of cadmium at least, these are dissociated in the kidney and may result in cadmium nephritis a reflection of the greater binding capacity of renal tissue for cadmium than BAL Citrate a chelating agent used for lead poisoning is metabolized by the body and is therefore relatively ineffective A list of some representative binding and chelating agents is shown in Table \XXI Their use in medicine is only beginning For example all antithyroid drugs have this common property suggesting their probable action

These considerations open up a wide field of thought on the mechanisms of disease and of drug actions Similar conclusions can be drawn when late toxic reactions of drugs are compared with structure The common denominator of the offending drugs appeared to be in chelation

Drug Reactions Late systemic reactions to drugs affect several organs and systems of which blood dyscrasias hepatitis and polyarteritis are the most serious (252) Most of the drugs causing fatal agranulocytosis as listed by

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1018. 1019. 1020. 1021. 1022. 1023. 1024. 1025. 1026. 1027. 1028. 1029. 1030. 1031. 1032. 1033. 1034. 1035. 1036. 1037. 1038. 1039. 1040. 1041. 1042. 1043. 1044. 1045. 1046. 1047. 1048. 1049. 1050. 1051. 1052. 1053. 1054. 1055. 1056. 1057. 1058. 1059. 1060. 1061. 1062. 1063. 1064. 1065. 1066. 1067. 1068. 1069. 1070. 1071. 1072. 1073. 1074. 1075. 1076. 1077. 1078. 1079. 1080. 1081. 1082. 1083. 1084. 1085. 1086. 1087. 1088. 1089. 1090. 1091. 1092. 1093. 1094. 1095. 1096. 1097. 1098. 1099. 1100. 1101. 1102. 1103. 1104. 1105. 1106. 1107. 1108. 1109. 1110. 1111. 1112. 1113. 1114. 1115. 1116. 1117. 1118. 1119. 1120. 1121. 1122. 1123. 1124. 1125. 1126. 1127. 1128. 1129. 1130. 1131. 1132. 1133. 1134. 1135. 1136. 1137. 1138. 1139. 1140. 1141. 1142. 1143. 1144. 1145. 1146. 1147. 1148. 1149. 1150. 1151. 1152. 1153. 1154. 1155. 1156. 1157. 1158. 1159. 1160. 1161. 1162. 1163. 1164. 1165. 1166. 1167. 1168. 1169. 1170. 1171. 1172. 1173. 1174. 1175. 1176. 1177. 1178. 1179. 1180. 1181. 1182. 1183. 1184. 1185. 1186. 1187. 1188. 1189. 1190. 1191. 1192. 1193. 1194. 1195. 1196. 1197. 1198. 1199. 1200. 1201. 1202. 1203. 1204. 1205. 1206. 1207. 1208. 1209. 1210. 1211. 1212. 1213. 1214. 1215. 1216. 1217. 1218. 1219. 1220. 1221. 1222. 1223. 1224. 1225. 1226. 1227. 1228. 1229. 1230. 1231. 1232. 1233. 1234. 1235. 1236. 1237. 1238. 1239. 1240. 1241. 1242. 1243. 1244. 1245. 1246. 1247. 1248. 1249. 1250. 1251. 1252. 1253. 1254. 1255. 1256. 1257. 1258. 1259. 1260. 1261. 1262. 1263. 1264. 1265. 1266. 1267. 1268. 1269. 1270. 1271. 1272. 1273. 1274. 1275. 1276. 1277. 1278. 1279. 1280. 1281. 1282. 1283. 1284. 1285. 1286. 1287. 1288. 1289. 1290. 1291. 1292. 1293. 1294. 1295. 1296. 1297. 1298. 1299. 1300. 1301. 1302. 1303. 1304. 1305. 1306. 1307. 1308. 1309. 1310. 1311. 1312. 1313. 1314. 1315. 1316. 1317. 1318. 1319. 1320. 1321. 1322. 1323. 1324. 1325. 1326. 1327. 1328. 1329. 1330. 1331. 1332. 1333. 1334. 1335. 1336. 1337. 1338. 1339. 1340. 1341. 1342. 1343. 1344. 1345. 1346. 1347. 1348. 1349. 1350. 1351. 1352. 1353. 1354. 1355. 1356. 1357. 1358. 1359. 1360. 1361. 1362. 1363. 1364. 1365. 1366. 1367. 1368. 1369. 1370. 1371. 1372. 1373. 1374. 1375. 1376. 1377. 1378. 1379. 1380. 1381. 1382. 1383. 1384. 1385. 1386. 1387. 1388. 1389. 1390. 1391. 1392. 1393. 1394. 1395. 1396. 1397. 1398. 1399. 1400. 1401. 1402. 1403. 1404. 1405. 1406. 1407. 1408. 1409. 1410. 1411. 1412. 1413. 1414. 1415. 1416. 1417. 1418. 1419. 1420. 1421. 1422. 1423. 1424. 1425. 1426. 1427. 1428. 1429. 1430. 1431. 1432. 1433. 1434. 1435. 1436. 1437. 1438. 1439. 1440. 1441. 1442. 1443. 1444. 1445. 1446. 1447. 1448. 1449. 1450. 1451. 1452. 1453. 1454. 1455. 1456. 1457. 1458. 1459. 1460. 1461. 1462. 1463. 1464. 1465. 1466. 1467. 1468. 1469. 1470. 1471. 1472. 1473. 1474. 1475. 1476. 1477. 1478. 1479. 1480. 1481. 1482. 1483. 1484. 1485. 1486. 1487. 1488. 1489. 1490. 1491. 1492. 1493. 1494. 1495. 1496. 1497. 1498. 1499. 1500. 1501. 1502. 1503. 1504. 1505. 1506. 1507. 1508. 1509. 1510. 1511. 1512. 1513. 1514. 1515. 1516. 1517. 1518. 1519. 1520. 1521. 1522. 1523. 1524. 1525. 1526. 1527. 1528. 1529. 1530. 1531. 1532. 1533. 1534. 1535. 1536. 1537. 1538. 1539. 1540. 1541. 1542. 1543. 1544. 1545. 1546. 1547. 1548. 1549. 1550. 1551. 1552. 1553. 1554. 1555. 1556. 1557. 1558. 1559. 1560. 1561. 1562. 1563. 1564. 1565. 1566. 1567. 1568. 1569. 1570. 1571. 1572. 1573. 1574. 1575. 1576. 1577. 1578. 1579. 1580. 1581. 1582. 1583. 1584. 1585. 1586. 1587. 1588. 1589. 1590. 1591. 1592. 1593. 1594. 1595. 1596. 1597. 1598. 1599. 1600. 1601. 1602. 1603. 1604. 1605. 1606. 1607. 1608. 1609. 1610. 1611. 1612. 1613. 1614. 1615. 1616. 1617. 1618. 1619. 1620. 1621. 1622. 1623. 1624. 1625. 1626. 1627. 1628. 1629. 1630. 1631. 1632. 1633. 1634. 1635. 1636. 1637. 1638. 1639. 1640. 1641. 1642. 1643. 1644. 1645. 1646. 1647. 1648. 1649. 1650. 1651. 1652. 1653. 1654. 1655. 1656. 1657. 1658. 1659. 1660. 1661. 1662. 1663. 1664. 1665. 1666. 1667. 1668. 1669. 1670. 1671. 1672. 1673. 1674. 1675. 1676. 1677. 1678. 1679. 1680. 1681. 1682. 1683. 1684. 1685. 1686. 1687. 1688. 1689. 1690. 1691. 1692. 1693. 1694. 1695. 1696. 1697. 1698. 1699. 1700. 1701. 1702. 1703. 1704. 1705. 1706. 1707. 1708. 1709. 1710. 1711. 1712. 1713. 1714. 1715. 1716. 1717. 1718. 1719. 1720. 1721. 1722. 1723. 1724. 1725. 1726. 1727. 1728. 1729. 1730. 1731. 1732. 1733. 1734. 1735. 1736. 1737. 1738. 1739. 1740. 1741. 1742. 1743. 1744. 1745. 1746. 1747. 1748. 1749. 1750. 1751. 1752. 1753. 1754. 1755. 1756. 1757. 1758. 1759. 1760. 1761. 1762. 1763. 1764. 1765. 1766. 1767. 1768. 1769. 1770. 1771. 1772. 1773. 1774. 1775. 1776. 1777. 1778. 1779. 1780. 1781. 1782. 1783. 1784. 1785. 1786. 1787. 1788. 1789. 1790. 1791. 1792. 1793. 1794. 1795. 1796. 1797. 1798. 1799. 1800. 1801. 1802. 1803. 1804. 1805. 1806. 1807. 1808. 1809. 1810. 1811. 1812. 1813. 1814. 1815. 1816. 1817. 1818. 1819. 1820. 1821. 1822. 1823. 1824. 1825. 1826. 1827. 1828. 1829. 1830. 1831. 1832. 1833. 1834. 1835. 1836. 1837. 1838. 1839. 1840. 1841. 1842. 1843. 1844. 1845. 1846. 1847. 1848. 1849. 1850. 1851. 1852. 1853. 1854. 1855. 1856. 1857. 1858. 1859. 1860. 1861. 1862. 1863. 1864. 1865. 1866. 1867. 1868. 1869. 1870. 1871. 1872. 1873. 1874. 1875. 1876. 1877. 1878. 1879. 1880. 1881. 1882. 1883. 1884. 1885. 1886. 1887. 1888. 1889. 1890. 1891. 1892. 1893. 1894. 1895. 1896. 1897. 1898. 1899. 1900. 1901. 1902. 1903. 1904. 1905. 1906. 1907. 1908. 1909. 1910. 1911. 1912. 1913. 1914. 1915. 1916. 1917. 1918. 1919. 1920. 1921. 1922. 1923. 1924. 1925. 1926. 1927. 1928. 1929. 1930. 1931. 1932. 1933. 1934. 1935. 1936. 1937. 1938. 1939. 1940. 1941. 1942. 1943. 1944. 1945. 1946. 1947. 1948. 1949. 1950. 1951. 1952. 1953. 1954. 1955. 1956. 1957. 1958. 1959. 1960. 1961. 1962. 1963. 1964. 1965. 1966. 1967. 1968. 1969. 1970. 1971. 1972. 1973. 1974. 1975. 1976. 1977. 1978. 1979. 1980. 1981. 1982. 1983. 1984. 1985. 1986. 1987. 1988. 1989. 1990. 1991. 1992. 1993. 1994. 1995. 1996. 1997. 1998. 1999. 2000. 2001. 2002. 2003. 2004. 2005. 2006. 2007. 2008. 2009. 2010. 2011. 2012. 2013. 2014. 2015. 2016. 2017. 2018. 2019. 2020. 2021. 2022. 2023. 2024. 2025. 2026. 2027. 2028. 2029. 2030. 2031. 2032. 2033. 2034. 2035. 2036. 2037. 2038. 2039. 2040. 2041. 2042. 2043. 2044. 2045. 2046. 2047. 2048. 2049. 2050. 2051. 2052. 2053. 2054. 2055. 2056. 2057. 2058. 2059. 2060. 2061. 2062. 2063. 2064. 2065. 2066. 2067. 2068. 2069. 2070. 2071. 2072. 2073. 2074. 2075. 2076. 2077. 2078. 2079. 2080. 2081. 2082. 2083. 2084. 2085. 2086. 2087. 2088. 2089. 2090. 2091. 2092. 2093. 2094. 2095. 2096. 2097. 2098. 2099. 2100. 2101. 2102. 2103. 2104. 2105. 2106. 2107. 2108. 2109. 2110. 2111. 2112. 2113. 2114. 2115. 2116. 2117. 2118. 2119. 2120. 2121. 2122. 2123. 2124. 2125. 2126. 2127. 2128. 2129. 2130. 2131. 2132. 2133. 2134. 2135. 2136. 2137. 2138. 2139. 2140. 2141. 2142. 2143. 2144. 2145. 2146. 2147. 2148. 2149. 2150. 2151. 2152. 2153. 2154. 2155. 2156. 2157

eight metals almost certainly present in a strongly bound form in their tissues did not change

BAL (2,3-dimercaptopropanol) a straight chain dithiol binds the following heavy metals in a chelate zinc chromium cadmium nickel, lead, antimony, arsenic, bismuth copper, mercury, gold (251) Substitution complexes on the sulphydryls are formed In the case of cadmium at least, these are dissociated in the kidney and may result in cadmium nephritis a reflection of the greater binding capacity of renal tissue for cadmium than BAL Citrate a chelating agent used for lead poisoning is metabolized by the body and is therefore relatively ineffective A list of some representative binding and chelating agents is shown in Table XXXI Their use in medicine is only beginning For example all antithyroid drugs have this common property suggesting their probable action

These considerations open up a wide field of thought on the mechanisms of disease and of drug actions Similar conclusions can be drawn when late toxic reactions of drugs are compared with structure The common denominator of the offending drugs appeared to be in chelation

Drug Reactions Late systemic reactions to drugs affect several organs and systems of which blood dyscrasias hepatitis and polyarteritis are the most serious (252) Most of the drugs causing fatal agranulocytosis as listed by

1. procaine amide and Tapazole contain pyridines amines amides nitroso or sulphydryl groups (253) Their solubilities and specificities for heavy metals however are not known to our knowledge Nonfatal leucopenia has occurred with arsenical compounds gold salts thiouracils hydantoins salicylates sulfonamides streptomycin and thiosemicarbazone which can displace or bind

TABLE VXXI—(continued)

| | |
|--------------------------------------|-----|
| Nitrite | |
| Thiocyanate | |
| Pyrocatechol | |
| Quinaldine | |
| Hydantoin | |
| Hydrazine | |
| Chelating Chemicals * | |
| Phytic Acid | |
| 2 ketogluconic acid | |
| Glycerophosphates | |
| Potassium gluconate | |
| Gallates | |
| Rubeanic acid and derivatives | |
| Guanidine carbonate | |
| Potassium ethyl xanthate | |
| Dimethyl glyoxime | |
| Uracils | |
| Oximes | |
| Diphenyl carbazide | |
| Diphenyl thiocarbazon | |
| Potassium thiocarbonate | |
| Cupferron | |
| Adipoin | |
| Some Reagents for Analysis of Metals | 256 |
| Zn Ferric cyanide | |
| 8-hydroxyquinoline | |
| Quinaldinate | |
| Sn Dinitro-diphenylamine sulfoxide | |
| Toluene dithiol | |
| Ag P-dimethylamino-benzalrhodamine | |
| Ni γ benzil-dioxime | |
| Dithiooxalate | |
| Dithiol | |
| Mo Thiocyanate | |
| Cu Quinosol | |
| Pyridine thiocyanate | |
| Cd β -naphthoquinoline | |
| Thiourea | |
| Benzoin-oxime | |

From chemical catalogues

TABLE VXXI—(continued)

| | |
|--------------------------------------|-----|
| Nitrite | |
| Thiocyanate | |
| Pyrocatechol | |
| Quinaldine | |
| Hydantoin | |
| Hydrazine | |
| Chelating Chemicals * | |
| Phytic Acid | |
| 2 ketogluconic acid | |
| Glycerophosphates | |
| Potassium gluconate | |
| Gallates | |
| Rubeanic acid and derivatives | |
| Guanidine carbonate | |
| Potassium ethyl xanthate | |
| Dimethyl glyoxime | |
| Uracils | |
| Oximes | |
| Diphenyl carbazide | |
| Diphenyl thiocarbazon | |
| Potassium thiocarbonate | |
| Cupferron | |
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| Cd β -naphthoquinoline | |
| Thiourea | |
| Benzoin-oxime | |

From chemical catalogues

causing shock 13 new ones appear which do not have this property and 13 of the above are represented. Bronchial asthma caused by 36 agents of which 19 are of plant or animal origin and unidentified structurally 11 caused by 14 containing possible metal complexing groups or metals. A similar situation appears among the agents causing severe late toxic skin reactions such as eczema urticaria exanthemata exfoliative dermatitis bullous eruptions and the like. Metals and binding agents appear frequently when the chemical structure is known.

Curiously enough serious local and systemic reactions are rare or absent among the drugs not containing metal reactive groups or producing them only on extensive hydrolysis. Sulfobromophthalein decholin, paredrine ether boric acid Banthine menthol quotate diocaine chloral hydrate morphine opium codeine digitalis are examples. On the other hand barbituric acid the basic constituent of many sedatives and a pyridine compound forms salts with metals. Metal binding by sulfanilic acid is well known (233). The instability of hydantoin hydrolyzing to metal binding hydantoic acid the metal binding properties of pyridines nitroso groups (dinitrophenol is a good example) cyanides amine and sulphydryl groups *semicarbazides* dicarboxylic acids thiols and sulfur-containing structures appear to be related to many forms of drug sensitivity. Therefore it is possible that trace metals may be involved in many reactions of sensitization and perhaps even in some forms of allergy. BAL (2,3-dimercaptopropanol) for example is a potent contactant. Although drug reactions vary widely in frequency such agents as dinitrophenol being very active and amines relatively inactive may be -

and sulfate etc.) the more likely

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and sulfate etc.) the more likely

TABLE XXXII

TRACE METALS FOUND IN MAN AND THEIR PROBABLE ROLES

| Essential | Possibly
Essential | No Known
Metabolic
Function | Metabolic or
Antimetabolic | Not Found
in Anti-
metabolic |
|-----------|-----------------------|-----------------------------------|-------------------------------|------------------------------------|
| Cobalt | Aluminum | Barium | Bismuth | Antimony |
| Copper | Selenium | Boron | Cadmium | Arsenic |
| Iron | Vanadium | Cesium | Chromium | Beryllium |
| Manganese | | Gallium | Gold | Thallium |
| Hydrogen | | Lanthanum | Lead | |
| | | | Nickel | |
| Zinc | | | Silver | |
| | | Tin | Titanium | |

Those in italics may be implicated in chronic diseases especially cardiovascular because of their prevalence in concentrations or known functions on enzyme systems.

and satisfying certain criteria for reactivity in enzyme mechanisms can be expected to have become essential for metabolism. We cannot say that living cells have learned to use new and less reactive elements in enzyme systems by a process of adaptation; the basic structures of atoms have not changed and life began by using the most suitable ones.

Because all food comes eventually from plants, an examination of the metallic content of plants is necessary. Local pastoral variations can be neglected. No metal can be expected to be essential for animals which does not occur in plants or in water. In Table XXXIII are the metals of interest in plants. Little aluminum, nickel, and no cadmium, tin, silver, gold, titanium, lead, or mercury is to be expected in animal tissues, while vanadium and the five known essential metals will be found. Obviously, if domestic animals or man show appreciable quantities of those which do not appear in plants, they must have come from unnatural sources.

To be classed as abnormal for our thesis, a metal

TABLE XXXII

TRACE METALS FOUND IN MAN AND THEIR PROBABLE ROLES

| Essential | Possibly Essential | No Known Metabolic Function | Metabolic or Antimetabolic | Not Found in Antimetabolic |
|-----------|--------------------|-----------------------------|----------------------------|----------------------------|
| Cobalt | Aluminum | Barium | Bismuth | Antimony |
| Copper | Selenium | Boron | Cadmium | Arsenic |
| Iron | Vanadium | Cesium | Chromium | Beryllium |
| Manganese | | Gallium | Gold | Thallium |
| Hydrogen | | Lanthanum | Lead | |
| | | | Nickel | |
| | | | Silver | |
| Zinc | | Tin | Titanium | |

Those in italics may be implicated in chronic diseases especially cardiovascular because of their prevalence concentrations or known functions on enzyme systems.

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To be classed as abnormal for our thesis a metal

a) should be found in human tissues from some areas of the world and not from others b) should not be found in plants or wild animals c) should affect some metallo-enzymes d) preferably should not be in the tissues of young infants e) should be introduced by the habits of Western Civilization into foods or beverages as a result of processing transportation or manufacture and f) should be poorly excreted cumulative and preferably showing organ specificity

Concentrations of the Essential Trace Metals in Man

Although many analyses have been done by various methods for single or several elements in blood tissues and urine (254-257) the first extensive systematic investigation on the content of both essential and abnormal trace metals in human tissues was made by Tipton and her co-workers. Using spark spectrographic methods with indium as an internal standard and densitometric photo-electric recording of plates Tipton analyzed 208 tissues from 24 persons dying suddenly in various areas of the United States for 18 metals (almost 4500 analyses) (251). A preliminary analysis of 42 autopsies from various places in this country showed similar but less quantitative results (258) while in a later series the findings were essentially the same (259).

In Table XXXIV are the mean concentrations in various tissues of the essential elements manganese cobalt copper zinc and molybdenum calculated roughly for total bodily amounts. Zinc is the most prevalent of the normal group in several times the concentration of any of the others. Essential cobalt was found in only five bodies sparsely scattered in small concentrations probably because of methodological limits and its presence in very minute quantities. These results appear comparable to those of Griffith *et al* for copper zinc and manganese on

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the basis of dry tissue in a much larger series (260)

Some organs concentrate certain metals others do not Zinc was found in every organ in concentrations of 4.4 to 300 mg/Kg being far highest in prostate then muscle liver kidney and heart and lowest in adrenal bladder brain testis lung and intestine Copper was concentrated in brain liver and spleen being lowest in muscle adrenal aorta intestine and testis Manganese in much smaller amounts was concentrated especially in liver with pancreas lung spleen and thyroid following quite far behind lowest organs were heart muscle testis and aorta Three of these four metals were found in all 258 specimens examined Molybdenum was absent in only half of the samples of muscle and testis a third of those of pancreas thyroid and lung most prostates and all but one brain but was found in concentrations of more than 0.18 mg/kg in all heart kidney and liver samples being by far the highest in liver In the concentrations detectable, molybdenum apparently is not essential for metabolism in all organs but three of the others may be

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may also be important in hemoglobin formation. A copper enzyme ceruloplasmin is found in concentrations of about 34 mg per 100 ml of serum. Several phenolic oxidases depend upon copper. pigmentation may be related to the content in skin and hair follicles. Copper is quite well retained by the body with some dependency upon intake, being slowly eliminated by way of the feces. Gallstones contain large amounts. No chronic copper poisoning has been described in human beings. Human milk is extremely low in content 0.04 mg/kg. As a rule American foods contain adequate amounts sometimes an excess since many insecticides and fungicides contain copper. The largest amounts 10 mg/kg or more are found in tea, coffee, cocoa, chocolates, nuts, liver, shell fish especially oysters, tomatoes and yeast. The least is found in milk, butter, cheese, refined sugar, honey, margarine, lard and suet.

Zinc This most prevalent of the trace metals in the human body is present in large quantities in most organs as seen in Table XXXIV. It is found in foods and is a requirement of plants, bacteria and fungi. Most modern fungicides are zinc chelating agents. Deficiency in soils causes diseases of both plants and animals although its prevalence makes animal diseases more uncommon. Foods with over 50 mg/kg are wheat germ, bran, oysters, beef, livers, gelatin and dried eggs; those which contain the least amount are fruits, chestnuts, green vegetables and fish. Chronic poisoning in man is not known. There have been several outbreaks of supposedly acute poisoning from foods stored in zinc lined receptacles but the contamination of zinc by cadmium makes it questionable that zinc itself was the cause. Symptoms of zinc and cadmium poisoning are identical i.e. violent gastroenteritis and zinc poisoning is most difficult to produce in animals.

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high content of iron in their livers. Apparently the bacteria in the rumen synthesize vitamin B₁₂ when cobalt is present. High requirements are indicated by the large doses of the vitamin necessary to cure this disease. Horses and pigs raised in the same deficient areas are not affected as their requirements are lower. Bacterial synthesis in the colon, as occurs in man, apparently does not lead to absorption of this vitamin, therefore it must be ingested as such. Copper deficiency has been implicated in certain anemias in infancy but no known diseases in adults have been described. Anemia has been produced in laboratory animals along with a slow rate of growth, impaired absorption of ingested iron, impaired mobilization of iron from tissues and impaired utilization of iron for hemoglobin synthesis have been found, as well as low cytochrome oxidase activity of the bone marrow. Cattle grazing on copper-deficient pastures show depigmented, abnormal hair, develop cachexia, anorexia and anemia; their bones become fragile; reproduction and milk production is decreased and they frequently die of cardiac failure. Young animals may become ataxic. Sheep show defective keratinization and hypochromic anemia. Lambs born of copper-deficient ewes develop swayback and ataxic and paralytic diseases characterized by diffuse demyelination of the central nervous system. Depigmentation has been produced in many species. Excesses or deficiencies of other trace elements may influence the disorders in cattle and sheep, especially of cobalt and molybdenum. Molybdenum deficiency prevents fixation of nitrogen by soil bacteria.

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TABLE IV
CONTAMINANTS AND CONTENTS OF ABNORMAL TRACE METALS WITH ORGAN SPECIFICITIES
(NET WEIGHT) (23)

[illegible]

Figures in parentheses indicate the per cent of total population in each age group.

ubiquitous elements tin nickel, chromium and silver (Table XXXVI)

The obvious conclusions are that relatively large amounts of cadmium are in American kidneys and aluminum and titanium in lungs while other metals are more or less evenly distributed. Furthermore there is weight for weight more of several abnormal metals in most organs than normal ones of high biological activity such as manganese copper and molybdenum. On the basis of mass alone these three tables show the following when the metals are arranged according to the periodic table. Silver is present in amounts equal to 2.2 per cent of copper cadmium equal to 12 per cent of zinc (50 per cent in the kidney) chromium equal to 61 per cent of molybdenum (and is more prevalent) nickel equal to 140 per cent of cobalt while there is more titanium tin and lead than manganese molybdenum and cobalt and there is more aluminum than copper. Thus the order in decreasing amounts is Zn Al Cu Cd Pb Ti Sn Mo, Ni Co, Cr Mn Ag B according to the present estimate (essential ones in italics). Traces of gallium were found in most lungs of bismuth in 21 samples of gold in 72 samples and of thallium in 6 samples.

In Tipton's second series of 24 autopsies from another (western) part of the United States (259) the findings were quite similar for the essential metals although there were somewhat less copper and zinc in most organs and molybdenum was largely confined to liver and kidney. Of those now considered abnormal cadmium appeared in liver and kidney in the same concentrations as in her first series but a large majority of other organs were lacking in this element. There was much less aluminum in all organs but lung (23 mg/Kg) and titanium was found in only a few bodies except for lung where its concentration

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(266) There were 4 kidneys and livers 3 lungs 2 spleens and 1 aorta heart intestine and muscle In contradistinction to adult tissues kidneys and livers and lungs contained no titanium cadmium or tin Aluminum was not concentrated in lung although it occurred in amounts of 0.3-1.0 mg/kg in most tissues less than that of adults Titanium was found in only one body in intestine kidney and muscle Nickel occurred in one other kidney and liver tin was in both spleens and the sample of muscle and aorta On the other hand boron was in all tissues but one kidney and liver chromium and silver were ubiquitous in adult concentrations as was lead but in smaller amounts than in adults Organ specificity as determined by concentration was not found consistently *

In the bodies of 3 older infants and children (7 weeks 10 months and 2 years) there was no titanium Nickel in traces was in 1 kidney tin was found in all tissues as was lead while silver occurred in 7 of 12 specimens Cadmium was present in the 10 month-old kidney (0.65 mg/kg) and in the 2 year-old (2.75 mg/kg) but not in the 7 week old one The essential metals were found in distributions and concentrations similar to those of adults Manganese was if anything more concentrated zinc less so while copper was comparable showing an affinity for liver Molybdenum was in all livers while cobalt was present in only two

Within the limits of these observations, and in view of what is known the following further conclusions can be drawn 1 Titanium nickel and cadmium are not essential to infant life but accumulate with age 2 Aluminum chromium silver and lead either qualify as essential trace metals or pass through the placental membrane Obviously titanium nickel cadmium and tin do not so pass

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Some of these metals accumulate with age in Americans others do not. In Table XXII Chapter V are shown examples. Obviously cadmium, titanium, nickel and tin in all tissues and aluminum in lung increase from little or none in infants to relatively higher concentrations at older ages. The striking examples are in cadmium and titanium.

Trace Metals in Tissues from Uncivilized People In order to ascertain more definitely what trace metals are essential and what are not, a small number of tissues from African natives in little contact with Western Civilization were obtained by Dr. Perry from Uganda and analyzed by Dr. Tipton (266). The ages ranged from 18 months to over 50 years; there were three under 10 and four over 40. None showed any evidence of atherosclerosis in the aorta or elsewhere; even fatty streaks were not seen. The causes of death were several. Six patients died of acute infections. No age trends in essential metals were apparent as is the case with Americans. The interesting findings lay in the absence of those which might be guessed to be products of Western Civilization: cadmium (in only one kidney), nickel and tin, and the much smaller amounts of silver, lead, chromium and possibly titanium (Table XXXVII).

Conclusions Therefore it becomes apparent that nickel, chromium, cadmium, lead, silver and tin are not essential elements but results of civilization, a conclusion which could be drawn from the analyses of children's tissues only for cadmium, nickel and titanium. The possibility of these six elements found in American tissues being toxic must therefore be considered. Common sense excludes silver because of its low concentrations. In addition, we cannot rule out the possible essential nature of aluminum, barium, strontium and for lung of vanadium and ti

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antimony We can add to our list of possibly toxic metals bismuth and cesium

Are these extraneous elements biologically active or inert? Could one or more of these abnormal elements displace an essential metal and thus lead to metalloenzyme inhibition or combine with sulphhydryl enzymes and so inactivate them (Table XXVIII)? If so the possibility of inhibition causing dysfunction leading to disease is considerable

METALS OF POSSIBLE BIOLOGICAL SIGNIFICANCE IN THE FIRST TRANSITIONAL GROUP

It is interesting that the transitional and nearby metals in the periodic table are those with most biological activity an expression perhaps of their structures (267) Other than the known essential trace metals of the first transitional group four might serve in metalloenzymes but have at present no known function i.e. titanium vanadium chromium and nickel Vanadium is found in all of the animal phyla is concentrated from sea water by tunicates as an essential oxygen carrier (268) is required by *aspergillus niger* (269) is concentrated in certain mushrooms (270) --

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10 mg/kg in all plants dry weight (271) The case for it having a function in mammals is good While chromium stimulates plant growth is present in all vegetables in concentrations of 10 to 1000 γ /kg dry weight and is in many human tissues evidence for its essential nature is doubtful Nickel is probably not required by mammals although plants contain traces The role of titanium is not known although it is found in almost all human adult lungs Those concentrated in certain organs may be of more significance in metabolism or in causing diseases

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Evidence for Vanadium Being an Essential Trace Metal

What evidence there is for vanadium being essential to mammalian metabolism is indirect but good. Aside from its use by ascidia which use it for oxidation-reduction reactions at a time when they are buried in mud, petroleum contains varying amounts of vanadium in a porphyrin form which has led to the hypothesis that animal organisms and not plants originated the formation of petroleum. It is found in mammalian tissues at a fairly good concentration, said to be 0.13 per cent dry weight, 12 mg/kg for invertebrates and 0.1 mg/kg dry tissue for vertebrates (268). While its occurrence may be a chance contamination, universal presence and three valence states (V^{III} , V^{IV} , V^{V}) with an ability to release energy similar to phosphorus make it likely that vanadium may be essential. Tipton found it only in the lung.

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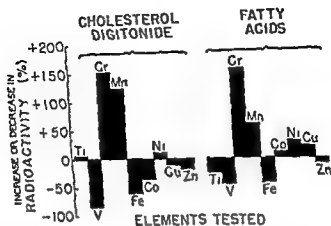


FIG 18 The effect of certain transition metal salts on the incorporation of C^{14} -carboxyl labeled acetate into cholesterol and fatty acids by surviving rat liver (From Curran G L *J Biol Chem* 210 765 1954)

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Normal urine contained less than 0.05 to 1.03 γ/L (mean <0.46), hypertensive urine less than 0.05 to 4.4 γ/L (mean 0.88). Treatment did not change the means significantly (0.67 to 0.71 γ/L) nor did hydralazine or EDTA cause a consistent loss.

Chromium in liver could stimulate cholesterol and fatty acid synthesis in man. There is as much, however, in infants as in adults. Only by analyzing many more tissues from primitive areas can one determine whether or not chromium can qualify as an essential metal or if not play a part in chronic disease.

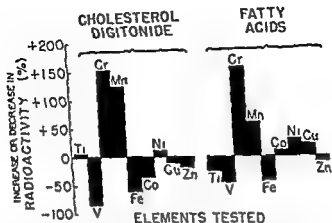


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Scandium and gallium are found in soils The traces of gallium in human lungs probably have been inhaled since gallium is present in all aluminum minerals Both are relatively unreactive compounds with only one valence state

Comment If one were forced to choose a single trace metal to undo the harmful effects of degenerative cardiovascular diseases vanadium would be that choice for the following reasons

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Silver Like tin silver is widespread occurring in every adult kidney and brain and in almost every other sample examined (225 of 258 specimens) (231). There was no tendency for accumulation with age and almost every young tissue contained it in adult concentrations (266). It was in all urine (0.8 γ/L . range 0.23-1.4) hypertensive urine contained little more than did normal (1.4 γ/L . range 0.3-4.6). Exposure to silver is constant in our society there is little or none in plants. Because of the small amounts found it is doubtful that enzymatic inhibition (on copper enzymes) if present is extensive enough to cause metabolic disorders.*

Lead There is lead in all human tissues at birth and during life. This toxic metal accumulates especially in bone and liver. As far as is known it is not an essential constituent of any living organism getting into food mainly from the use of its compounds on plants and from vessels in which food is manufactured transported or stored. Shell fish may absorb lead from sea water contaminated with drainage from factories and animals from sprayed plants. African tissues had little.

A knowledge of the coordination number of a metal, the shape of its chelate and its periodic group allows a reasonably accurate if indirect method of predicting displacement of a known essential metal and inactivation of its enzyme. Conversely by isotopic studies unknown

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cause pulmonary fibrosis (from inhalation) (282-285) renal damage (286) this toxic metal is under considerable suspicion as a cause of chronic disease. Of all the exogenous abnormal metals found in adult American tissues cadmium appears the most toxic. It is obviously cumulative. Supposedly 40 mg by inhalation can cause death in man which is strange since the total content of adult bodies is about 120 mg and the lethal dose in rabbits by injection is 3 mg/kg (LD_{50}) (81). Hepatic and renal lesions are prominent features of acute poisoning in rabbits and rats; cardiac hypertrophy is universal (286). Proteinuria and renal lesions occur in exposed workers (287). There must be obvious differences between acute and chronic effects in man especially when this metal accumulates for a life time. The protein in the urine is not albumin since it appears on the heat test but is not precipitated by Esbach's reagent (287). Cadmium causes aminoaciduria in man (288) •

The source of the cadmium may lie in zinc for it is a constant contaminant of zinc ores. There is probably one per cent or more in the galvanizing grade (Prime Western) as indicated by the following specifications adopted in 1911 by the American Society for testing materials last

Cadmium causes increased excretion of the following amino acids in man exposed industrially: glycine, alanine, glutamine, tyrosine, lysine, histidine, methyl histidine. All of these except possibly lysine can act as donors of ammonia. Furthermore, serine excretion was increased 9.5 and threonine 33 times. The amount of cadmium in the urine was in the same range 12-33 $\mu\text{g/L}$ (average 20 $\mu\text{g/L}$) as we have found for hypertensive individuals (308). Cadmium was unique among four heavy metals (U, Pb, Cd, Hg) studied by Clarkson and Kench (238) who believed that it specifically inhibited the renal tubular reabsorption of these amino acids. An alternative and to us preferable explanation lies in the specific inhibition of decarboxylases by cadmium thus preventing the first step of renal amino acid metabolism.

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Renal decarboxylase is inhibited *in vitro* at a lower concentration of cadmium than that present in adult kidney Other enzymes known to be inhibited *in vitro* are leucine aminopeptidase carnosinase succinic dehydrogenase choline oxidase (Table XXVIII) possibly through sulfhydryl binding If other metalloenzymes are specifically inhibited such as vitamin B₆ enzymes it is obvious that effects of low concentrations could be profound and in the case of vitamin B₆ result in a conditioned local deficiency

As in the case of zinc and lead cadmium can be dissolved in slightly acidic media Therefore foods and waters coming in contact with cadmium could become contaminated by traces There are three possible sources 1) Water is usually piped in American houses through galvanized zinc coated iron pipes If soft aerated in municipal water stations to contain carbon dioxide and chlorinated appreciable quantities of zinc lead and presumably cadmium could be dissolved from the galvanized coat If hard however insoluble carbonates are laid down on the coating protecting it from solution and corrosion Water softeners probably would not soften water enough to corrode zinc Chlorinated water even when hard takes up zinc.* 2) Carbonated beverages are acidic and will take up zinc lead and presumably cadmium from galvanized or zinc lined

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The source of cadmium which does not occur in plants is obviously in the products of Western Civilization *

Other Metals Analyses for other commonly occurring possibly toxic metals such as arsenic antimony and bismuth of group V A have revealed no striking accumulations in human tissues. There may be as much as 0.3 parts per million of arsenic in man much of it in hair and nails derived from fish and sea foods or from contaminants of food. Arsenic displaces phosphorus in essential phosphate mechanisms but the amounts are probably too small to cause functional disorders and habituation or tolerance develops. Antimony can gain access to foods from enamels solders tin foil rubber and insecticides. The normal amounts in human tissues are not known but presumably it also displaces phosphorus. Bismuth was found by Tipton in only a few bodies in small amounts in liver and kidneys (12 of 18 cases) and is probably not to be considered of universal import. Mercury appeared in a surprisingly large number of kidneys analyzed by Griffith *et al* from patients with congestive heart failure who had supposedly never received diuretics containing this metal (260)

Cardiovascular Implications Aluminum and strontium were present in all samples of American heart muscle. These metals plus lead and tin were found in all aortas. In kidney there was the additional metal cadmium in liver these five and silver. In adrenals were the same six and

Preliminary single analyses of five bottled drinks revealed: a carbonated water .4; a popular carbonated drink 11; a citrus drink 1; a grape juice 1.5; a whiskey 5.5 in parts per billion. Three of these values are considerably higher than those of normal urine. The grape juice contained relatively much nickel tin and lead.

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What good will it do our patients if the abnormal metals are removed from their bodies? We do not know. The subject of metals and chronic diseases is barely beginning to be appreciated. Forbes *et al* say for example. It is conceivable that the continuous ingestion of infinitesimal amounts of these metallic elements present in natural foods leading to their very gradual accumulation in the tissues may contribute to the processes of senescence in proportion to the degree with which they are combined with tissue proteins (apoenzymes) and the extent to which they inhibit or distort enzyme action in such combinations (290). While this may be true it is more likely that many of the diseases common only to our Civilization may be caused by the nonessential metals contaminating our foods, as a result of our industrial habits. We may be pleasantly surprised at the therapeutic results of their removal. Scleroderma has already been completely relieved in at least one instance by EDTA (291).

A logical therapeutic regimen within the limits of present-day vision is a concerted effort at removal by relatively nonspecific chelators followed by replacement of essential metals so removed. Generalized deficiency states of the essential metals iron cobalt copper and molybdenum is probably unlikely under such a regimen. manganese and zinc may require replacement. Too much of an essential metal however probably can cause as much disorder as too little. When deficiencies are recognized they can be treated.

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Chapter VII

SOME MECHANISMS IN ATHEROSCLEROSIS

INTRODUCTION

ALTHOUGH atherosclerosis is usually a disease of Western Civilization it has been observed in nomads. To begin to understand its pathogenesis one must consider the influences which civilization may contribute and those which can lead to the disease in uncivilized people. A brief discussion in a monograph on hypertension is justifiable for hypertensive patients are prone to develop the disease, treated hypertensive patients die mainly of its effects (319), hypertension accelerates its progress and there may be some basic factor common to both.

Atherosclerosis can occur without diastolic hypertension. Severe degrees of the disease in the aorta causing loss of elasticity produce systolic hypertension because the pipes are hard but do not of themselves cause elevated diastolic pressure. Contrariwise hypertension can persist without significant atherosclerosis especially in China (8, 313, 440).

In 1941 Snapper made some pertinent comments which are lately being appreciated (8). Another point which must be specially mentioned is the infrequency of arteriosclerosis in North China. The rarity of arteriosclerosis is proved by the scores of middle aged patients dying from all sorts of diseases showing hardly any sclerosis at autopsy. Extensive arteriosclerosis certainly does occur in North China but the thickened inelastic aorta with the widely

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PATHOGENETIC FACTORS

According to Friedman *et al* (314) the following schema invokes the multiple etiological factors and illustrates the pathogenesis of atherosclerosis

$$\text{Time} \times \begin{matrix} \text{Intrinsic (?) } \\ \text{Intimal} \\ \text{Derangement} \end{matrix} \times \begin{matrix} \text{Quantitative and} \\ \text{Qualitative Alter} \\ \text{ation of Plasma} \\ \text{Lipids Including} \\ \text{Cholesterol} \end{matrix} \times \text{Blood Pressure} = \text{Atherosclerosis}$$

We will consider each of these factors separately

1 Blood Pressure Rarely does long standing diastolic hypertension in Caucasians exist beyond the age of 40 without atherosclerotic lesions being found in aorta major arteries or coronaries Experimental hypertension is necessary to induce atherosclerosis in the rat a resistant animal and is desirable in the dog Fat in serum can be made to infiltrate the walls of arteries under high pressure especially if the intima is injured (315) Even in normotensive persons lesions develop at the sites of changes of pressure such as the mouths of the renal arteries in the Circle of Willis and at the bifurcation of the aorta (316 317) Atherosclerotic gangrene seldom occurs in the arm but is frequent in the leg where the hydrostatic pressure of the blood in the upright position is added to the blood pressure (318) These lesions are believed to be the result of pressure causing deposition of insoluble cholesterol or its esters subintimally either by forcing them into the vessel walls or preventing their diffusion out after entrance via the vasa vasorum

2 Intimal Injury Mechanical injury to the intima of dogs results in the formation of atheromata (320 322) It is difficult to understand how injury can occur at a normal pressure although acute hypertension in animals (323)

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metal interference (with decarboxylases for example) that in liver by marginal concentration of vitamin B₆, excessive saturated fatty acid load and possibly metals. There is no evidence for a generalized deficiency state except for the high incidence of dandruff in the population believed by some to be dependent upon vitamin B₆ and fatty acid imbalance.

3 Trace Metals The synthesis of cholesterol and fatty acids by surviving rat liver can be influenced by metals of the first transitional group (Fig. 18). Chromium and manganese have a pronounced enhancing action, vanadium a depressant one (248). Vanadium also promotes unsaturation of phospholipid fatty acid and oxidation of the double bond opposed by manganese (Table XXXVIII). There is no evidence, however, that chromium is implicated in the hypertensive process. In American tissues hepatic chromium is much less concentrated than manganese, a known lipotropic agent (231-259) (Chapter VI). Many metals directly affect oxidation of unsaturated fatty acids *in vitro*. Hydrogenation to harden or saturate them is accomplished commercially mainly by copper and nickel; sizeable quantities enter the fat during processing (256). Cadmium, however, inhibits at least one vitamin B₆ enzyme, DOPA decarboxylase (Chapter V), although it does not affect hepatic synthesis of cholesterol in the rat (331). Obviously we need to know much more about the effects of abnormal metals on the enzymes concerned in fatty acid and steroid synthesis.

A significant series of experiments were done by Curran and Costello in rabbits (280). Hypercholesterolemia was induced by feeding cholesterol at the 3 per cent level for 4 weeks. On resumption of a normal diet, cholesterol levels usually fall slowly. Half the rabbits were fed vanadium as VOSO₄ (0.05 per cent) for 6 weeks. There were

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Hypertension and atherosclerosis however may be interrelated in a more fundamental fashion than by mechanical excessive filtration of cholesterol through intima by the high pressure when there are adequate cholesterol levels in blood. 1) A conditioned vitamin B₆ deficiency may involve both disorders. 2) abnormal trace metals may not only affect the hypertensive process but increase cholesterol synthesis. At this point the reader may wonder whether or not the author has an obsession with vitamin B₆ and its functions. Upon careful thinking in terms of enzymatic mechanisms this coenzyme continually obtrudes itself into possible schemata derived from experimental and clinical data both in hypertension and in fatty acid metabolism.

We must turn to epidemiologic data for evidence that there is no common denominator of these two diseases. Some atherosclerosis but no hypertension has been found in Alaskan Eskimoes (332) the incidence may be smaller than in whites. Hypertension is extremely common in Hawaiian sugar plantation workers as is atherosclerosis but severe coronary sclerosis is less frequent than in Caucasians (333). Atherosclerosis is said to be prevalent in Kirghiz nomads as is contracted kidney (from hypertension?) (334). Snapper observed hypertension but little

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THE ROLE OF FAT AND OTHER LIPIDS

Let us review modern ideas on the pathogenesis of the lesions other than the factors already discussed. Most of the recent interest in the subject has centered on fats. Quite a case can be made for the role of cholesterol which is largely carried by lipoproteins as a strong link in the chain of reactions leading to the formation of plaques. The subject has had its ups and downs since 1914 but probably is here to stay. As Aschoff so aptly put it: "From plasma of low cholesterol content no deposition of lipoids will occur even though the mechanical conditions are favorable" (327).

Normal Cholesterol Levels in Blood What is the normal level of blood cholesterol? That is a difficult question to answer. The levels found in Europeans and especially Americans may not represent normal values but rather average values in a population subject to the disease. If so we should look elsewhere at healthy adults to determine our normal standards and thus our therapeutic aims in controlling and reversing the atherogenic tendencies of

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Considerable information comes from studies in other than Western countries (Table XXXIV). If these values for blood cholesterol be correct as there is little reason to doubt, the normal range is 120 to 160 mg per cent. Higher values may be ascribed to dietary influences or their concomitants. That environment and an increasing standard of living may affect blood lipids was well shown by Toor *et al* in their study of recent immigrants to Israel compared to immigrants living 20 years or more in that country (338) (Table XL).

In Table XLI are shown some wide variations in total cholesterol and other lipids in blood done by analytic methods which are considered quite accurate from various Western countries. The variations are unexplained. Page *et al* tried to check the differences between their analyses done in New York (339) and Boyd's done in Ontario (340). They state "our results for cholesterol determined in the presence of the other lipids are likely to be low rather than high. For the fact that our normal cholesterol values range so much higher than those of Boyd (in Ontario) and of Gardner and Gainsborough (in England) we therefore lack an explanation. We can find no source of error for our results and none is obvious for theirs." Since Boyd's normal subjects were taking the standard high fat diet customary in this country (340) it is possible that an environmental factor not present in England and Ontario but influencing levels in New York was operating.

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169 ♂ | 54
50 | |
| Man and Peters | Connecticut | 1933 | 207 ♂ | | 222 |
| Boyd | Ontario | 1935 | 177 ♂ | 52 | 185 |
| Page <i>et al</i> | New York | 1935 | 232 ♂ | 32 | 181 |
| Peters and Man | Connecticut | 1943 | 194 | 54 | 240 |
| Gertler and Garm | New York | 1950 | 224 | | 299 |
| Gubner and Ungerleider | New York | 1949 | 211 | | |
| Keys | Minnesota | 1949 | 218 | | |
| Kornerup | Denmark | 1950 | 203 | 55 | 172 |
| Block <i>et al</i> | Minnesota | 1951 | 181 | | 234 |
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From Page *et al* (339) and Katz and Stamler (356)

acid esters of cholesterol regardless of the length of the carbon chain melt at higher than body temperatures the lowest μ for oleate (44.5°C) and linoleate (42°C) compare stearate (82.5°C) and palmitate (90°C) (348) Therefore variations in solubility and melting point may determine deposition of these esters in the lesions Solubilities of the cholesterol esters of β -lipoproteins believed to be of atherogenic importance (350) are not known

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IODINE NUMBERS OF SERUM LIPIDS WHITE PATIENTS

| Patient | Age | Sex | Total
Cholesterol
mg/100 ml | I ₂
No | Atherosclerosis
Diagnosed | Other conditions |
|---------|-----|-----|-----------------------------------|----------------------|------------------------------|---|
| T K | 64 | ♀ | 96 | 71 | + | Lobar pneumonia convalescent |
| T N | 65 | ♂ | 101 | 94 | + | Pulmonary insufficiency bronchiectasis |
| T I | 59 | ♂ | 106 | 56 | + | Rheumatic heart disease |
| T S | 54 | ♂ | 111 | 70 | + | Myocardial infarction |
| T S | 58 | ♂ | 119 | 82 | + | Myocardial infarction emphysema |
| L J | 67 | ♂ | 124 | 89 | | Idiopathic hyperthyroidism |
| L D | 62 | ♀ | 131 | 63 | + | Metastatic carcinoma of stomach |
| L N | 68 | ♂ | 133 | 97 | + | Inferior vena caval obstruction |
| R S | 68 | ♂ | 134 | 61 | + | Cerebral thrombosis |
| R S | 49 | ♂ | 148 | 70 | + | Pulmonary fibrosis and insufficiency |
| R B | 67 | ♂ | 182 | 124 | + | Hypertension |
| M J | 50 | ♂ | 191 | 61 | + | Hypertension |
| T G | 58 | ♂ | 206 | 78 | + | Angina pectoris |
| T B | 48 | ♂ | 210 | 88 | + | Metastatic carcinoma of breast |
| T B | 48 | ♂ | 231 | 126 | + | Angina pectoris |
| T B | 74 | ♂ | 242 | 71 | + | Nephrotic syndrome |
| T G | 43 | ♂ | 550 | 162 | | Ameloidosis nephrotic syndrome |
| T N | 60 | ♂ | >500 | 102 | + | Cerebral thrombosis hypotension |
| J T | 44 | ♂ | | 84 | | Vascular tumor of brain |
| J B | 65 | ♂ | | 76 | + | Hypertension aneurysm of Circle of Willis |
| J C | 53 | ♂ | | 70 | | Chronic cystitis |
| J H | 54 | ♂ | | 62 | + | Diabetes Parkinsonism |
| A H | 63 | ♂ | | 76 | + | Carcinoma of prostate |
| V V | 71 | ♂ | | 78 | + | |
| O W | 70 | ♂ | | | | |
| Mean | 60 | | | 81 | | |

From data of Ferry, Schwartz, Hager and Schroeder

Note: The iodine number of human depot fat is 64 (348) and cholesterol is 65.8. The mean iodine number of fatty acids in plasma of normal Chinese is 156.6 (8).

TABLE XLIII
IODINE NUMBERS OF SERUM LIPIDS WHITE PATIENTS

| Patient | Age | Sex | Total
Cholesterol
mg/100 ml | I ₂
No | Atherosclerosis
Diagnosed | Notes |
|---------|-----|-----|-----------------------------------|----------------------|------------------------------|---|
| K | 64 | ♀ | 96 | 71 | + | Lobar pneumonia convalescent |
| P | 65 | ♂ | 101 | 94 | + | Pulmonary insufficiency bronchiectasis |
| F | 59 | ♂ | 106 | 56 | + | Rheumatic heart disease |
| I | 54 | ♂ | 111 | 70 | + | Myocardial infarction |
| M | 68 | ♂ | 119 | 82 | + | Myocardial infarction emphysema |
| L | 67 | ♂ | 124 | 89 | + | Idiopathic hypertrophy |
| D | 62 | ♂ | 131 | 63 | + | Hyperthyroidism |
| W | 68 | ♂ | 133 | 97 | + | Metastatic carcinoma of stomach |
| R | 68 | ♂ | 134 | 61 | + | Inferior vena caval obstruction |
| S | 49 | ♂ | 148 | 70 | + | Cerebral thrombosis |
| B | 67 | ♂ | 182 | 124 | + | Pulmonary fibrosis and insufficiency |
| H | 50 | ♂ | 191 | 61 | + | Hypertension |
| M | 55 | ♂ | 206 | 78 | + | Angina pectoris |
| S | 58 | ♂ | 210 | 88 | + | Metastatic carcinoma of breast |
| G | 48 | ♂ | 231 | 126 | + | Angina pectoris |
| I | 74 | ♀ | 242 | 71 | + | Nephrotic syndrome |
| T | 45 | ♂ | 550 | 162 | + | Arteriosclerosis nephrotic syndrome |
| N | 60 | ♂ | >500 | 102 | + | Cerebral thrombosis hypertension |
| I | 44 | ♂ | | 84 | + | Vascular tumor of brain |
| T | 65 | ♂ | | 76 | + | Hypertension aneurysm of Circle of Willis |
| M | 53 | ♂ | | 70 | + | Chronic cystitis |
| C | 54 | ♂ | | 62 | + | Diabetes Parkinsonism |
| I | 63 | ♂ | | 76 | + | Carcinoma of prostate |
| A | 71 | ♂ | | 78 | + | |
| V | 70 | ♂ | | | | |
| O | | ♂ | | | | |
| Mean | 60 | | | 81 | | |

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 Note: The iodine number of human depot fat is 64 (348) and cholesterol is 65.8 The mean iodine number of fatty acids in plasma of normal Chinese is 156.6 (8)

in the blood. What they are and what they are made of is of the greatest importance.

The lipoproteins carry steroid hormones, cholesterol and its esters, carotene or vitamin A, α -tocopherol and acetal lipid (containing hydroxyl groups) (352, 353, 387). Most (75 per cent) of the free cholesterol in serum is in the β -lipoprotein fraction as is the esterified fraction (73 per cent) while less (55 per cent) of the phosphorus is in this fraction. Barr found somewhat lower values in β -lipoproteins (354, 355). Thus, increase in the cholesterol:phospholipid ratio suspected to be of atherogenic significance means in terms of lipoproteins that with relatively less phospholipid than cholesterol the β -lipoprotein fraction will be increased in the proportion of 1:1.35. Gofman finds that particles of the S_{10-20} classes have weight ratios of cholesterol to phospholipid as high as 1:1.3 (356).

Exogenous Cholesterol. There is no evidence that a diet containing reasonable amounts of cholesterol (up to 1.8 Gm per day or the equivalent of four eggs) influences the level of blood cholesterol (357). Feeding healthy volunteers (358) or patients (359) up to ten times that amount causes insignificant changes in plasma levels.* Actually at 200 mg per 100 ml blood there is about 8 Gm in circulation with an additional 3 to 4 Gm in liver and a considerable amount in other tissues. While exogenous cholesterol probably little affects plasma levels in man, the reverse, i.e. restricting the dietary intake to very low values, does decrease plasma levels since all dietary cholesterol is contained in fatty foods which therefore need

* It is possible to block some of the intestinal absorption of exogenous cholesterol by plant sterols such as β -sitosterol in large doses. The effect on plasma cholesterol, however, is either insignificant, or significant to a very minor degree.

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usually contain unsaturated fatty acids. This is not true of fish oils which must be largely unsaturated or short chain because of the low melting point essential for mobility of the animal at low temperatures. Actually fish fat contains several very long chain unsaturated fatty acids.

There are three habits largely common to the U S A and some European countries which tend to raise the dietary intake of saturated fats (202 348 360) 1) Since 1920 animals fattened for slaughter have been fed high carbohydrate diets in order to lay down a hard fat. Meat from animals eating unsaturated vegetable fats is oily and housewives do not like to buy it the melting point is low 2) For many years vegetable fats (unsaturated) have been commercially hardened often by a copper or nickel catalyst in order to provide shortenings or margarine which are solid at room temperatures 3) The consumption of milk butter and cheese has increased milk fats contain shorter chain saturated fatty acids and are believed to be atherogenic (356)

Relation of Dietary Fats to Cholesterol Why does an excessive intake of hard or saturated fats cause atherosclerosis? The following information is known

1 Animals lay down in their tissues part of the fat ingested. This has been demonstrated in all mammals but man. Pigs fed very long chain high melting point fatty acids may crack in the cold. Unnatural fats (odd numbered carbon atoms or optical isomers of natural fats) can be recovered from the bodies of animals to which they are fed in amounts from 10 to 25 per cent (348)

2 Cholesterol esters can be formed of the type of fat in the diet. Thus stearic or even unnatural fatty acid esters of cholesterol can be recovered when a specific fat is fed (348)

3 The esters of cholesterol in blood usually contain

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TABLE XLV

COMPOSITIONS OF CORN COTTONSEED OLIVE OILS AND BUTTER*

| | Corn | Cottonseed | Olive | Butter |
|----------------------------|---------|------------|-------|--------|
| Iodine number | 103-129 | 90-110 | 79-90 | 26-38 |
| Saturated acids (%) | 12-18 | 21-32 | 9-19 | 30-43 |
| Oleate | 21-49 | 19-36 | 64-86 | 28-41 |
| Linoleate | 34-61 | 34-56 | 4-15 | |
| Linolenate | 0-2.9 | 0 | 0 | 0 |
| Arachidonate | 0 | 0 | 0 | 0 |
| Squalene (mg %) | 28 | 8 | 383 | 0 |
| Ergosterol | + | + | 0 | + |
| Sitosterol | + | + | 0 | |
| Stigmasterol | + | | | |
| Rate of enzymic hydrolysis | 1 | 2 | 3 | |
| Tocopherol (mg %) | 87-250 | 83-110 | 3-30 | |

* After Deuel (348) and Eckey (447) Contents vary with climate soil and seed

cholesterol has been shown to be squalene a hydrocarbon with six double bonds having the empirical formula $C_{30}H_{50}$ (362) Squalene is found in the unsaponifiable fraction of several but not all fish oils and only one plant oil olive oil (0.41-0.54 per cent) Other vegetable oils contain only very small amounts (peanut oil 0.07 per cent) Animals fed labelled squalene synthesize cholesterol 50 times as efficiently as when given labelled acetate (362) Squalene is not converted to fatty acids as is acetate An other precursor of cholesterol is provitamin D₂ or 7-dehydrocholesterol widespread in foods but in small quantities

Effect of Various Fats on Blood Cholesterol Levels in Man One can gain some information on the relationship of the type of fat ingested to the level of cholesterol in plasma by human experiments in which dietary fat was markedly increased (Table XLVI) If these results are valid an examination of the table points at once to specific dietary factors or the lack of them which alter cholesterol

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XLVII) Arachidonic acid a normal component of animal tissues lecithins cephalin phosphatides and fats is an other essential fatty acid formed from linoleic probably by a vitamin B₆ enzyme system (349)

Therefore the factor in certain vegetable fats (and not others) which lowers blood cholesterol may not lie in the presence or absence of unsaturated fatty acids themselves

TABLE XLVII

ESSENTIAL FATTY ACID CONTENT OF SOME EDIBLE OILS (%)

| Food | Linoleic | Linolenic | Production† |
|-------------|----------|-----------|-------------|
| Linseed | 15-43 | 40-53 | 2.2 |
| Peanut | 47-72 | 0 | 3.9 |
| Sunflower | 44-75 | 0.1 | 2.0 |
| Sesame | 40-48 | 0 | 1.5 |
| Soy bean | 52.0 | 2.3-11 | 3.8 |
| Coconut | 1-2 | 0 | 4.6 |
| Animal fats | + | 0 | 17.8 |
| Rapeseed | 12-16 | 7-10 | 3.3 |
| Palm | 6-11 | 0 | 3.3 |

* After Eckey (447) †Estimated World 1951 billions of lbs

but in the linolenic or other specific fatty acid content. The cholesterol lowering diets of Kinsell *et al* contain nuts in large amounts (363). The fat from some nuts especially walnuts contains linoleic and linolenic acids (348). In this respect Kinsell's diets (364-365) contained soybeans soy lecithins soy sauce corn oil and walnuts all containing linolenic acid while this fatty acid has not been found in peanuts almonds and cashew nuts (348). The hydrogenated oils in margarine Crisco and peanut butter as well as cottonseed peanut and olive oil which apparently do not contain linolenate were also given in spite of these fats at least two of which usually raise blood cholesterol it fell. Brain extract probably cephalin which

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Pyridoxal and Trace Metals The amount of vitamin B₆ in the diet has a definite influence on essential fatty acid metabolism in animals. Vitamin B₆ deficiency and essential fatty acid deficiency in rats resemble each other grossly and each factor will partly alleviate the other. There are however fundamental differences in enzymes in the two

TABLE XLIX
COMPARISON OF ESSENTIAL FATTY ACID AND PYRIDOXINE
DEFICIENCIES IN RATS (384)

| Function | Organ | Essential
Fatty
Acid | Pyridoxine |
|--------------------------|---------|----------------------------|-------------|
| Respiration | Liver | Increased | |
| Cytochrome oxidase | Liver | Increased | Increased ± |
| Succinic oxidase | Liver | No Change | No Change |
| Phosphate esterification | Liver | Decreased | Decreased |
| Glutamic dehydrogenase | Liver | Decreased | Decreased |
| Butyric dehydrogenase | Liver | Decreased | No Change |
| Succinic dehydrogenase | Liver | Decreased | No Change |
| Glutamic decarboxylase | Brain | — | Decreased |
| Arachidonic synthesis | Carcass | Decreased | Decreased |
| Hexaenoic synthesis | Carcass | Decreased | Decreased |
| Octanoate oxidation | Carcass | — | Decreased |

conditions (Table XLIX). Apparently vitamin B₆ is essential for desaturating partly unsaturated fatty acids such as linoleic further to synthesize arachidonic and in metabolizing linolenic to hexaenoic acids. Linoleic is a precursor of arachidonic and linolenic of the hexaenoic acids (349).

deficiency or saturated fatty acid excess. Thus the members of the Russian Orthodox Church eat nothing of animal origin during Lent. Advent and on Wednesdays and Fridays and use oils high in linolenic acid. Roman Catholics by custom supply themselves with adequate essential fatty acids on Fridays and during Lent but do not restrict other animal fats. Mohammedans have strict dietary laws during Ramadan. In terms of deposition of lipid these religious habits probably do no harm in maintaining or restoring the integrity of the intima.

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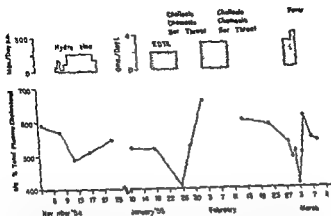
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Fatty
Acid | Pyridoxine |
|--------------------------|---------|----------------------------|-------------|
| Respiration | Liver | Increased | |
| Cytochrome oxidase | Liver | Increased | Increased ± |
| Succinic oxidase | Liver | No Change | No Change |
| Phosphate esterification | Liver | Decreased | Decreased |
| Glutamic dehydrogenase | Liver | Decreased | Decreased |
| Butyric dehydrogenase | Liver | Decreased | No Change |
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| Octanoate oxidation | Carcass | — | Decreased |

conditions (Table XLIV). Apparently vitamin B₆ is essential for desaturating partly unsaturated fatty acids such as linoleic further to synthesize arachidonic and in metabolizing linolenic to hexaenoic acids. Linoleic is a precursor of arachidonic and linolenic of the hexaenoic acids (349).

deficiency or saturated fatty acid excess. Thus the members of the Russian Orthodox Church eat nothing of animal origin during Lent. Advent and on Wednesdays and Fridays and use oils high in linolenic acid. Roman Catholics by custom supply themselves with adequate essential fatty acids on Fridays and during Lent but do not restrict other animal fats. Moslems have strict dietary laws during Ramadan. In terms of deposition of lipid these religious habits probably do no harm in maintaining or restoring the integrity of the intima.

LT 44 NEPHROSIS



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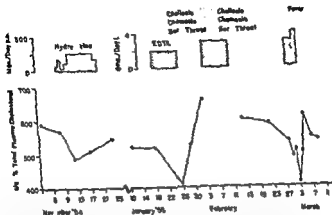


FIG 20 Effects of oral hydralazine and intravenous EDTA on plasma cholesterol levels. L. F. 44 years of age was seen in October 1954 because of mild exertional dyspnea and ankle edema for six months. At 7 years of age he had Marie Strumpell arthritis and at 25 years of age migratory polyarthritides without urinary symptoms. Nephrosis was clinically evident and amyloidosis was proved by renal punch biopsy. To lower his plasma cholesterol hydralazine was begun with out evident clinical improvement. In a further effort to lower his plasma cholesterol three courses of parenteral EDTA were given. On the sixth day of this first course of therapy slight inflammation of the mucous membranes and a magenta tongue were observed and he complained of soreness about his mouth and gums. By the final day cheilosis, chemosis, scrotal inflammation and pustular lesions over the face and trunk had appeared. Within a week the lesions had vanished and a second course of EDTA was begun. On the fourth day stomatitis reappeared and within 7 days the same syndrome was present again necessitating the discontinuation of therapy. The 3-day final course produced no such lesions, however fever immediately followed the dosage increase to 4 Gm. Cholesterol values for the second course were not plotted because such a low plasma level was attained that a laboratory error was suspected (303 mg per 100 ml on a single determination). The changes in cholesterol preceded clinical toxicity (From Perry H. M. Jr and Schroeder H. A. J. Chronic Dis. 2:520, 1955.) Metal excretion in Table XXX, p. 160.

we would expect little or no atherosclerosis especially of our coronary arteries

There appears to be something in certain but not all vegetable fats which lowers blood cholesterol markedly in man while animal fats hydrogenated vegetable fats and other vegetable fats with a lower iodine number raise plasma cholesterol. As a first guess this substance may be linolenate an essential fatty acid. If that is so Europeans and Americans may be suffering from a relative essential

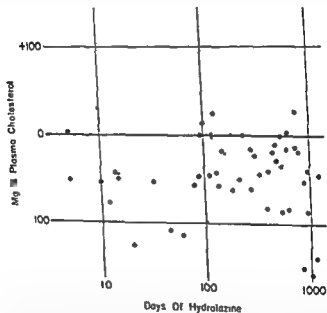


FIG 92 Effect of oral hydralazine on total fasting plasma cholesterol in 110 hypertensive patients. Changes in cholesterol concentrations before and after hydralazine are plotted against the length of therapy. Each large dot indicates a patient with an initial cholesterol level of more than 215 mg per 100 ml plasma. Each small circle indicates a patient with lower initial values below 211 mg per 100 ml plasma (From Perry H M Jr., and Schroeder H A J *Chronic Dis* 2 50 1955)

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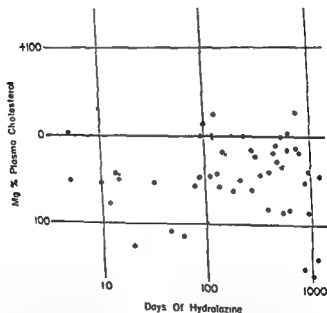


FIG. 92 Effect of oral hydralazine on total fasting plasma cholesterol in 11⁹ hypertensive patients. Changes in cholesterol concentrations before and after hydralazine are plotted against the length of therapy. Each large dot indicates a patient with an initial cholesterol level of more than 215 mg per 100 ml plasma. Each small circle indicates a patient with lower initial values below 211 mg per 100 ml plasma. (From Perry H. M. Jr., and Schroeder H. A. *J. Chronic Dis.* 2:570, 1955.)

| | | | |
|----------------------------------|---|----------|-------------------|
| Intimal Injury due to | Increased Saturated | | |
| a) Vitamin B deficiency | over Unsaturated | | |
| b) Excessive hypertension | × Fatty acid esters of | × Blood | = Atherosclerosis |
| c) Normal pressure differentials | cholesterol lipoproteins and phospholipids Increased synthesis or decreased destruction of cholesterol due to metals or fatty acid deficiency | Pressure | |

The nature of the vitamin B₆ deficiency and its possible relation to trace metals has already been discussed. The plasma lipids under consideration include a) Cholesterol esters which are said to be usually of unsaturated fatty acids although esters of equal length saturated fatty acids are lighter and more insoluble. Dietary excess of the latter could influence their nature. b) Lipoproteins or protein fatty acid complexes the nature of which are unknown. The saturated fatty acid esters should be lighter and more insoluble than their unsaturated counterparts. If so they should centrifuge more slowly (or float more rapidly). A lipoprotein with a specific flotation rate of S₁ 0.10 if its fatty acid became saturated should theoretically change to the S₁ 10.20 class unless rearrangement of the molecule took place. c) Phospholipids the fatty acid components of which depend partly perhaps on dietary intake but usually are formed of unsaturated fatty acids in functioning tissue (brain and liver).

Effect of Sex. For some unknown reason ~~women~~ women are quite immun

The disorder however after the menopause as in men. Coronary occlusion in a normotensive menstruating woman was formerly extremely rare although cases are now appearing. The degree of aortic atherosclerosis however shows little sex

| | | |
|---------------------------|---|------------------------------------|
| Intimal Injury due to | Increased Saturated
over Unsaturated | X Blood Pressure = Atherosclerosis |
| X a) Vitamin B deficiency | Fatty acid esters of | |
| b) Excessive hypertension | cholesterol lipo- | |
| c) Normal pressure | proteins and phospho- | |
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fluctuations can occur (377) A persistently high level is atherogenic a momentary low level may not reflect the true state of affairs in terms of intimal exposure There are conflicting opinions and data but the opposing views can be resolved by realization that a) cholesterol levels fluctuate and unless consistently elevated values may be meaningless 2) when a patient is sick the levels fall 3) the full lesions of atherosclerosis develop only after prolonged constant or intermittent hypercholesterolemia

In this chapter we have spoken of trace metal imbalances conditioned vitamin B₆ deficiencies and essential fatty acid deficiencies We have emphasized that these deficiencies are relative conditioned and local to one or at most a few enzyme systems There is no practical way however of reversing vitamin B₆ deficiencies at the present time The administration of 50 mg of pyridoxal hydrochloride daily to many patients has not resulted in a detectable fall in blood cholesterol The administration of at least two trace metals cobalt and manganese in large daily doses have not caused clinical changes detectable by ordinary laboratory methods Only by chelating agents have we been able to affect blood levels favorably (180)

The several pathogenetic factors outlined by Friedman *et al* should be affected simultaneously if we are to expect cessation of the process or at the best reversal Whatever is making the intima injured so that plaques are formed should be opposed as an approximation pyridoxine in adequate doses is required until more is known The abnormally high cholesterol levels in blood should be reduced by dietary influences and chelating agents if possible Elevated diastolic pressure should be controlled at normotensive levels Under these conditions some reabsorption of plaques which are not too scarred might be expected

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4 Diastolic normotension must be achieved and maintained whenever possible A compromise is hazardous merely modifies the disease promotes drug tolerance and does not allow eventual reduction of dosage

5 The use of any ganglionic blocking agent the action of which does not last for 24 hours requires that blood pressure be measured before each dose in order to prevent a) hypertension b) hypotension and c) to provide as constant a blood level as possible throughout the day and night Varying requirements and absorption necessitate varying dosages according to the prevailing levels of blood pressure

6 Arterial hypertension due to increased generalized vasospasm is a disorder or a disease The patient either has it or has not If he has severity varies widely from slight to marked Therapy should be applied when both patient and physician want to control the disease If therapy is not applied the responsibility rests on the physician that the disease is not doing or going to do harm

EVALUATION OF PATIENT FOR DRUG THERAPY

The first question to be answered is Has the patient hypertension? A diastolic pressure of 90 mm Hg or over (measured by the disappearance of Korotkoff sounds) is strongly suggestive in fact usually indicative of generalized vasospasm in the absence of tachycardia polycythemia or coarctation of the aorta When persistent it suggests chronic hypertension when relieved by relaxation it suggests the prehypertensive state

The second question is How severe or sustained is the

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primary organic renal diseases adrenal dysfunction or emotional crises

For a thorough work up evaluation of the cardiac status requires a study of the symptoms electrocardiographic tracing for left ventricular hypertrophy strain patterns or old myocardial infarction and roentgen or fluoroscopic examination of the heart In actual practice only signs of a previous coronary occlusion are important indications for cautious therapy but physicians are often gratified to watch enlarged hearts slowly become smaller and abnormal electrocardiographic tracings revert to normal under continuous therapy

Renal status is evaluated most easily by routine urinalysis and the intravenous injection of phenol red (PSP) with urine specimens obtained 15 30 and 60 minutes after injection The test is simple and reliable The bladder need not be emptied before the test although the first specimen may show a somewhat smaller amount of PSP* for unknown reasons (Reabsorption of PSP by bladder wall has not been ruled out) Adequate hydration is essential for accurate values The urinary concentration test is impractical on an outpatient basis owing to difficulties in restricting the amount of dietary water If the 15-minute PSP excretion is less than 10 to 15 per cent azotemia may be suspected

Retinoscopy is essential in all cases The appearance of exudative or hemorrhagic retinitis is often a poor prognostic sign making treatment mandatory The best method for grading fundal changes is that of Keith and Wagener

In a series of 39 medical students paired for the test with bladder empty the 15-minute excretion was 32.5 per cent with bladder full, 30.9 per cent The normal values with bladder usually empty were 15 minutes 32.5 per cent 30 minutes 21.2 per cent 60 minutes 17.0 per cent with a total of 70.7 per cent

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 - a Tumors of the pedicle*
 - b Aneurysms*
- 6 Diminution of the calibre of the renal arteries
 - a Congenital malformations hypoplasia*
 - b Atherosclerosis, with atheroma of the main renal artery (common)*
- 7 Disorders of the urinary tract
 - a. Obstructive disorders
 - (1) Lithiasis*
 - (2) Hydronephrosis (usually infected)*
 - (3) Pyonephrosis
 - (4) Congenital malformations*
 - (5) Prostatic hypertrophy*
 - (6) Uterine prolapse
 - (7) Pelvic tumors (fibromyomata)*
 - b Pyelonephritis (common)*
- 8 Venous obstruction
 - a External compression of renal vein
 - b Congestive heart failure*

The following intrarenal diseases must be considered

- 1 Inflammatory vascular lesions
 - a Disseminated lupus erythematosus*
 - b Polyarteritis nodosa*
 - c Syphilis
 - d Thromboangitis obliterans
- 2 Inflammatory renal lesions
 - a Glomerulonephritis*

The following endocrine diseases can influence hypertension

- 1 Hypophyseal tumors and hyperfunction*
- 2 Adrenal cortical and medullary tumors and hyperplasia*

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EVALUATION OF GENERALIZED VASOSPASM
IN HYPERTENSIVE STATES

It is of little more than academic interest what the underlying pathogenetic factors in a state of severe hypertension may be except when chronic pyelonephritis can be treated with antibiotics (often with little success) or recurrences of glomerulonephritis prevented by antibiotics designed to abort upper respiratory tract infections. It also matters little what the type of renal disease contributing to the vasospasm may be pyelonephritis glomerulonephritis secondary arteriolar nephrosclerosis or even polycystic disease. What do matter are the relative influences of neurogenic nephrogenic or adrenocortical factors in causing the vasospasm for the relative amounts of different drugs required will differ according to the amount of renal ischemia present. Therefore it is a good plan to group cases according to several stages of the disease dependent upon the amount of vasospasm one finds and its lability.

The degree of lability of the vasospasm is the factor which determines these stages. Complications such as cerebral vascular accident and coronary arterial occlusion can occur in any stage mild severe or normotensive as they are caused not directly by vasospasm but by an associated disease atherosclerosis. The fact that this other disease can be influenced by the severity of the hypertension i.e. the vasospasm has little to do with therapeutic measures aimed at vasospasm. Therefore classifications based partly upon atherosclerotic damage are valid for purposes other than the choice of drugs or procedures such as prognostic implications and for surgical risk. One would not use the most potent drugs in a patient with hemiplegia or congestive heart failure who exhibited severe atherosclerosis and mild hypertension, one would use them however in a patient with severe but asymptomatic

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Serious secondary atherosclerotic complications may or may not be present if so about 30 to 40 per cent may be dead in 3 years. The ocular fundi are Grade I or II renal function is normal or nearly normal and the blood pressure is roughly 180/100 to 220/120 mm Hg during rest in bed. Reserpine plus fairly large doses of hydralazine (300 to 400 mg per day) will control about half of these cases eventually the remainder require the addition of ganglionic blockade. With time individuals in this stage uniformly exhibit reversal of the process and marked reduction of dosage in 2 to 3 years a majority can be maintained on reserpine alone and a few will be in a complete but probably temporary remission.

Stage III is made up of individuals with Grade II to III (Keith Wagener) ocular fundi with or without occasional hemorrhagic and exudative lesions with severe generalized vasospasm and hypertension not relieved by heavy sedation (sodium amytal). Renal function is adequate but usually reduced. Serious atherosclerotic complications may or may not be present. The blood pressure is usually 200/120 to 270/160 mm during rest in bed. In this stage which usually carries a poor prognosis (40 per cent dead in 3 years) ganglionic blockade plus adequate doses of hydralazine (500 mg or more per day) are essential for control. Reserpine may or may not be added mainly for its sedative action in smoothing out variations in blood pressure caused apparently by emotional lability in the presence of incomplete and irregular ganglionic blockade. Therapeutic results are good 95 per cent surviving 5 years with considerable eventual reduction in dosages in most.

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Reduction in dosage will often alleviate the usual depressive effects of the agent and may reduce the number of nightmares, but nasal stuffiness can be most annoying. Epistaxis induced by the drug usually necessitates discontinuation. The time-tested sedatives are the only alternatives to replace reserpine if it cannot be used.

We have seen four patients whose severe hypertension was cured for several months in that all drugs had been discontinued.

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Use of Protoveratrine One can begin this agent in doses of 0.2 mg three times a day increasing by 0.2 mg per dose until nausea or vomiting appears (395). The dose causing nausea is then reduced by 0.1 or 0.2 mg and the others gradually increased to the point of nausea. The emetic effect appears within an hour after the dose often sooner. Wide swings of blood pressure occur with a rise at night. This agent cannot be given effectively every 4 hours as tolerance soon develops only to disappear with a few hours rest. To be completely effective

These developments stimulate speculation. If psychosomatic influences are blocked in one somatic nervous pathway the sympathetic perhaps

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blood pressure appeared to rise at end of the period. G. C. same in a 54-year-old man with severe aortic atherosclerosis who after 1 week achieved only a fair response and 120 to 140 mm. Hg diastolic pressure at levels higher than those achieved with reserpine. This diastolic pressure reduction in average daily blood pressure when reserpine 10 mg a day was added. Control had been previously increased on two occasions by adequate doses (From Schroeder H. A. *Am J Med* 17:540 1954)

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(From Schroeder H. A. *Am J Med* 17:540 1954)

the average level of

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1 Blood pressure is measured by competent nurses every 4 hours day and night and charted

2 Initial dose is given every 4 hours if the blood pressure is above a chosen level; usually 140 mm systolic. It is not given if the blood pressure is below that level. Slightly higher "omit" levels are used in the cases of atherosclerotic or azotemic patients: 150 to 170 mm Hg. Initial doses which are usually safe to give to patients with severe hypertension are: Hexamethonium chloride 125 mg, Pentolinium tartrate 20 mg, Chlorisondamine 10 mg, Mecamylamine 2.5 mg

3 If the desired normotension is not achieved, each dose is raised by increments amounting to the initial dose daily until 4 or 5 days have passed. Thus each dose given every 4 hours will be: Hexamethonium chloride 500 to 750 mg, Pentolinium tartrate 150 to 200 mg, Chlorisondamine 50 to 75 mg, Mecamylamine 15 to 20 mg. By this time intermittent normotension should have been achieved. (In order to change intermittency to more even control, hydralazine must be added at this point (Fig 27).) Each dip in systolic pressure gives the physician confidence in the lowest levels tolerable without cardiovascular accident.

4 Doses are then given on a sliding scale dependant on the level of blood pressure. If normotension is desired

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MB 743 NEUROGENIC HYPERTENSION

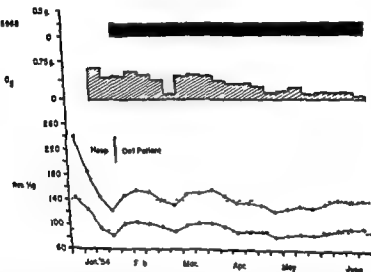


FIG 26 Examples of adequate control of blood pressure by giving adequate doses of ganglionic blocking agents (hatched area pentolinum bitartrate C₆) and hydralazine (solid black area 5968). In the case of H J in hospital control was poor at first until doses were raised sufficiently to achieve normotension. Each point represents the mean of six measurements. Diastolic normotension was achieved. H O₂. Note increase in blocking agent required at 100 mm Hg.

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MB # 43 NEUROGENIC HYPERTENSION

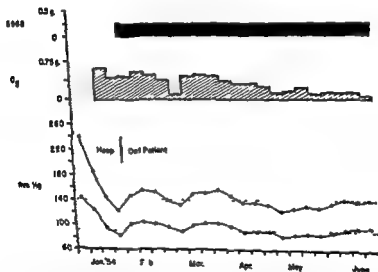


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tension Standing pressures are avoided The night dose is omitted leaving eight hours of uninterrupted sleep

5 Parasympatholysis should be treated A nightly laxative and magnesium citrate if the bowels have not moved by mid morning will usually promote a daily evacuation It is important to prevent distension of the intestines (404)

Precautionary measures against obstruction of a hollow viscus already partially obstructed should be taken Abdominal scars prostatic hypertrophy, frequent rhinitis, are warning signs of possible trouble from this source They are usually less severe than the disease being treated When the drugs cannot be tolerated protoveratrine can be substituted with good results Surgical sympathectomy, of course does not carry this hazard Prostatic obstruction may require surgery

Use of Hydralazine This drug is given almost always in conjunction with either ganglionic blockade (Fig 28) or another milder agent acting on nerves (423) Because of initial side reactions mainly attributable to its antihistaminase action which are lessened with nerve acting drugs it is begun at doses of 25 mg every 4 hours raising the dose to 50 75 and 100 mg every 4 hours on 3 successive days It is given with the blocking agent Thus 500 mg a day is the usual dose in severe hypertension we have had to give as much as 10 Gm for short intervals These large doses may cause hydralazine disease in 10 per cent of patients after 6 months In general larger doses are given for greater nephrogenic components to the vasospasm smaller doses when the neurogenic component is large It is unreliable when used alone (189 396)

High fever aching and malaise appearing during the first few weeks of administration of hydralazine requires discontinuation or marked reduction of dosage Fortunately such sensitive individuals are rare Angina pectoris

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can be made worse (or relieved) by hydralazine. A compromise partial control of hypertension by neurogenically acting drugs plus perhaps restriction of dietary sodium may provide some measure of vascular safety which while not ideal may lengthen life. In our experience patients with severe hypertension are rarely intolerant to this agent when it is first given.

Hydralazine disease appearing after 6 to 24 months of ingestion of fairly large doses necessitates two courses. Stopping the offending agent entirely results in return of hypertension. In these patients the mortality rate from hypertensive causes is 10 per cent. Large doses of ganglionic and hypothalamic blocking agents with or without protoveratrine usually fail to control the hypertension adequately. Wide swings from high to low levels take place daily. This situation is about the most difficult to meet in therapy and we have no solution. Low salt diets or thiocyanate might be used. Sodium azide has been valueless (Fig 29). Closely related analogues of hydralazine have caused recurrences of the disease and chemically less related ones have been relatively worthless.

Hazards of severe restriction of dietary salt are well known. The nephrosclerotic kidney is a salt losing kidney to some extent and hyponatremia with renal failure (the low salt syndrome) can be induced by limiting the intake to a point less than obligatory urinary losses. Borderline renal function predisposes to this usually fatal condition (397-399) (Fig 30).

The second choice involves marked reduction of the dose and the possible addition of cortisone until symptoms subside. The disease resembles in part a phenomenon of depletion. By small doses blood pressure can be controlled although L.E. preparations may remain positive. The disease remains in a subclinical lupoid stage and

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Before discharge measurement of blood pressure with the patient seated causes the amount of ganglionic block

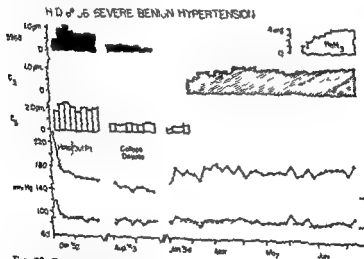


FIG. 29 Examples of hydralazine (collagen) disease with special reference to blood pressure.

hydralazine

Note strict normotension when hydralazine disease was once established. A sulfur containing compound was used. The pressure that of appear but not of 6 35

■ upon the time scale

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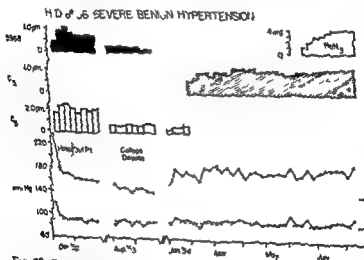


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ing agent automatically to adjust itself as postural effects occur. The usual result of omission of the night dose is a rise in the morning resting or basal pressure. The patient is taught to take his own blood pressure five times a day before each dose and record it on special charts. He is instructed on the actions of the drugs and their side effects. He leaves the hospital on the same schedule which was designed to prevent both hypertension and hypotension. By keeping a daily record trends can be observed which are invaluable for efficient therapy. In our clinic we examine a patient one month after discharge from hospital and then at 3 to 6-month intervals if he is doing well. Patients seldom complain of the inconvenience which takes about 15 minutes a day but they do object to the cost of the drugs.

Treatment of Crises In hypertensive crises (pulmonary edema, cerebral edema, toxemia of pregnancy) requiring parenteral administration, two lines 20 mm apart are drawn across the graphic chart at the level at which systolic pressure is to be maintained. After initial lowering of blood pressure by a small dose of a blocking agent, blood pressure is measured every hour and a subcutaneous injection of the full effective dose given if it is above the upper line, half the dose if between the lines and none if below the bottom line. Changes in total dosage must be made often. The second day the two lines are drawn 20 mm lower. Thus a patient with encephalopathy (wet brain) may have his pressure reduced from 300 mm Hg to 220 to 200 mm the first day, 200 to 180 mm the second day, and 180 to 160 mm the third day. Usually oral medication becomes possible long before this time. The pressure must be reduced more drastically when there is pulmonary edema. We prefer parenteral ganglionic blocking agents to parenteral hydralazine because of their shorter

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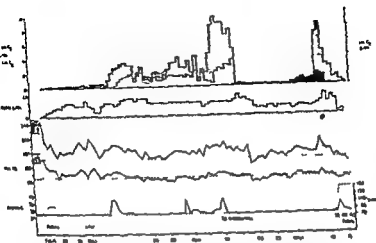


FIG 31 Medication and vital signs during hospitalization of a 52 year-old white male with malignant hypertension and pre treatment azotemia. The upper bar graph indicates the daily dose of autonomic blocking agent. The open bars represent oral pentolinium tartrate (po C_3). The cross hatched bars represent parenteral pentolinium tartrate (im C_3) and the solid bars represent parenteral hexamethonium chloride (im C_3). The potency of oral pentolinium tartrate approximates that of intramuscular hexamethonium chloride however the scale for intramuscular pentolinium tartrate has been expanded to allow for its greater effect. The lower bar graph indicates oral hydralazine intake per day. Daily blood pressure averages are shown each value being the mean of at least 6 and often as many as 24 readings taken with the patient in a sitting position. The stippled area to the left indicates the pre-treatment range of blood pressure. The line graph at the bottom of the figure is a schematic representation of the vital signs. The solid line shows the temperature in degrees centigrade which was below 37° except for three bouts of pyrexia. The dotted line shows the pulse in beats per minute which was always below 80 except for two episodes of tachycardia. The first two and three values

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in Press (1957)

J. L. Hunt, R. M. and Thomas W. A. *Am J Med*

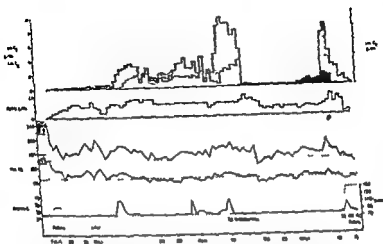


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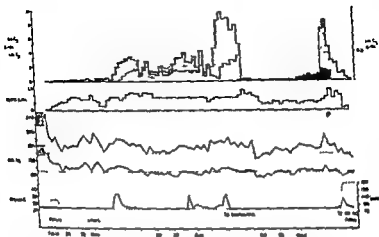


FIG 31 Medication and vital signs during hospitalization of a 52 year-old white male with malignant hypertension and pre treatment azotemia. The upper bar graph indicates the daily dose of autonomic blocking agent. The open bars represent oral pentolinium tartrate (po C_2). The cross-hatched bars represent parenteral pentolinium tartrate (im C_2) and the solid bars represent parenteral hexamethonium chloride (im C_2). The potency of oral pentolinium tartrate approximates that of intramuscular hexamethonium chloride however the scale for intramuscular pentolinium tartrate has been expanded to allow for its greater effect. The lower bar graph indicates oral hydralazine intake per day. Daily blood pressure averages are shown each value being the mean of at least 6 and often as many as 24 readings taken with the patient in a sitting position. The stippled area to the left indicates the pre treatment range of blood pressure. The line graph at the bottom of the figure is a schematic representation of the vital signs. The solid line shows the temperature in degrees centigrade which was below 37.5 except for three bouts of pyrexia. The dotted line shows the pulse in beats per minute which was always below 80 except for two episodes of tachycardia. The figures indicate tachypnea with any daily average values above 30 breaths per minute being noted. The word failure denotes the three periods of cardiac decompensation. Note the very high doses necessary once escape has occurred. Patient died. (From Perry H. M. Jr., O'Neal R. M. and Thomas W. A. *Am J Med* in Press 1957)

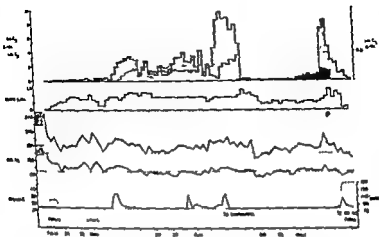
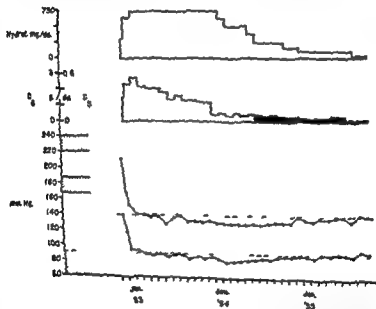


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stricted moderately d) The patient is readmitted to the hospital and restabilized e) Pheochromocytoma is suspected in patients whose blood pressures fluctuate widely and cannot be controlled Reduction in dosage is not possible for those who keep themselves moderately hypertensive even after 3 years Those who do best are those who attain and maintain normotension (Fig 33) (406)

JC # 34



— and dotted lines are for a 34-year-old white male of pre-treatment

indicate the drug intake the open area representing hydralazine the dotted hexamethonium (C_6) and the solid pentolinium (C_5). Note that the scale is different for the two methonium compounds since the second is approximately five times more potent than the first. (From Perry H M Jr and Schroeder H A. *Circulation* 13 528 1956)

abolished this within a few days. Salt can be added to the diet in from 2 to 6 months time. Also in a few weeks digitalis can be eliminated (Fig. 34). Only a rare individual continues to require digitalis and dietary restriction of salt. We presume that these patients suffer from myocardial fibrosis due to atherosclerosis. Heart failure with only a moderate hypertension and much coronary arterial disease however is only moderately affected.

1 b) Abnormal electrocardiographic patterns indicative of left ventricular strain revert to normal within several months. Patterns suggestive of left ventricular hypertrophy revert to normal in some but not in all cases. This may take 1 to 4 years. Enlarged hearts often but not always become smaller in roentgenograms. Time 1 to 5 years (406).

2 a) A few weeks after the start of therapy the progression of renal damage due to arteriolar nephrosclerosis is halted. Unpredicted was a gradual return of depressed renal function in many but not all cases. This occurs in from 1 to 4 years (405).

2 b) In from 1 to 2 weeks albuminuria diminishes or disappears. When caused by pre-existing organic renal disease it remains at lessened quantities.

2 c) In azotemic individuals nitrogen retention remains static or diminishes unless initial values are over about 60 mg per 100 ml of nonprotein nitrogen in the blood (Somogyi zinc precipitate corresponding to 75 to 90 mg per cent by the phosphotungstic acid precipitate method). Time weeks or months. In those with higher values azotemia usually but not always progresses to uremia rarely however we have seen relatively acute elevations to 130 to 160 mg per cent return to much lower levels. This may occur after 3 weeks or more (Fig. 35-36).

2 d) Ocular fundi revert to normal. Hemorrhages are

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D. M. P. H. BALDWIN HYPERTENSION WITH URICACIA (POLYCYSTIC KIDNEYS)

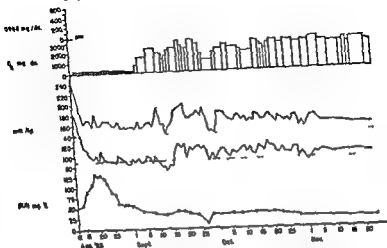


FIG 36 Medication blood pressure and nitrogen retention during hospitalization. The solid bars represent oral hydralazine (5968). The cross hatched bars represent parenteral and the open bars oral hexamethonium chloride (C_6). The parenteral dose has been multiplied by 10 in order partially to compensate for the much greater efficacy of this route of administration. Each of the points on the blood pressure curve is the average of at least six and initially as many as 24 determinations. All were made with the patient supine. Note that azotemia is shown in terms of blood urea nitrogen rather than total nonprotein nitrogen.

Except for life long enuresis this 18-year-old white male was entirely well until 3 days before he entered the hospital. His mother had died with polycystic kidneys. Pyrexia and malaise were the initial symptoms followed by lethargy, emesis, disorientation and coma. Physical examination revealed in addition papilledema, hemorrhagic retinitis, minimal cardiomegaly and a pre systolic gallop. Roentgenologic examination suggested polycystic kidneys and 3 plus albuminuria was found. After returning home the patient did very well. He was working when last seen in July 1955 at which time his physical examination including fundoscopic examination was normal. His urine contained no protein. His antihypertensive regimen called for a maximum dose of 750 mg oral hexamethonium chloride and a constant dose of 100 mg of hydralazine every four hours. His sitting blood pressure at home averaged 160/80 mm. Hg. (From Perry H. M. Jr. and Schroeder H. A. *Circulation* 14:105 1956.)

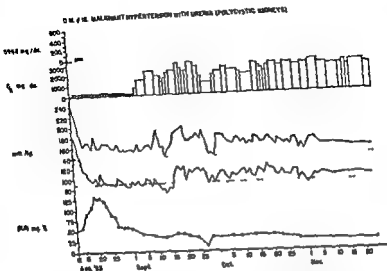


FIG 11 Medication blood pressure and nitrogen retention during hospitalization. The solid bars represent oral hydralazine (5968). The cross hatched bars represent parenteral and the open bars oral hexamethonium chloride (C_6). The parenteral dose has been multiplied by 10 in order partially to compensate for the much greater efficacy of this route of administration. Each of the points on the blood pressure curve is the average of at least six and initially as many as 24 determinations. All were made with the patient supine. Note that azotemia is shown in terms of blood urea nitrogen rather than total nonprotein nitrogen.

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absorbed in 2 to 6 weeks soft cotton wool exudates disappear in 1 to 4 weeks papilledema slowly regresses in 4 to 12 weeks and hard waxy exudates and scars shrink to nothing in 1 to 3 years

3 a) Atherosclerotic complications are less frequent In from 1 to 11 weeks angina pectoris usually disappears although rarely it becomes initially worse

3 b) The incidence of coronary occlusion appears somewhat lower (after 3 to 5 years) although this disease ac

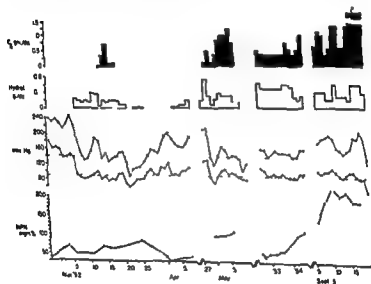


FIG 37
hypertension
been stat
f 11 - -

increased. Lower That of L. T. a 48 year-old man improved at first but azotemia later rapidly progressed to death. Pylonephritis was found at autopsy the kidneys together weighed 105 Gm.

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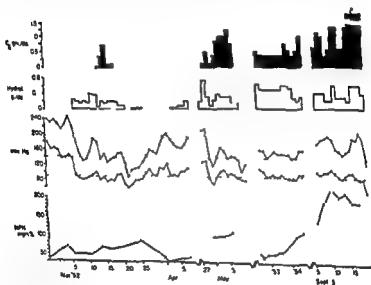


FIG 57
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C H -

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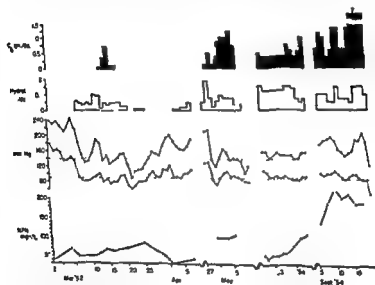


FIG 37 Two directions of progress in azotemia and malignant hypertension. Upper The condition of G. B., a 54-year-old man has been static or improving slowly and he has been able to work full time.

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72 mg

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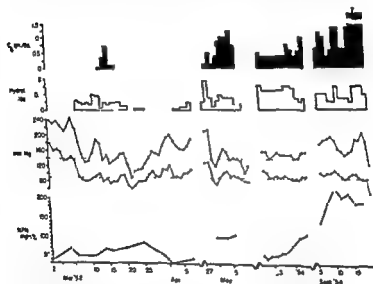


FIG. 37 Two directions of progress in azotemia and malignant hypertension. Upper The condition of G. B., a 54-year-old man has been static or improving slowly and he has been able to work full time. Lower That of L. T., a 48-year-old man improved at first but azotemia later rapidly progressed to death. Pyelonephritis was found at autopsy: the kidneys together weighed 105 Gm.

sponding well to ganglionic blockade alone can be expected to respond to surgery even though the usual lumbodorsal sympathectomy only removes 50 to 60 per cent of the nerves. Operation therefore does not become the method of choice when medical measures fail for the opposite holds true i.e. drugs will work when surgery has failed. The one advantage of surgical over chemical sympathectomy is the lack of bother to the patient when the result is successful.

According to the data of White (421) when cardiovascular complications occur in hypertensive patients the mortality is high. Left ventricular weakness and failure cerebrovascular accidents angina pectoris and myocardial infarctions cause a 3 year mortality rate of 82 per cent and a 10 year mortality rate of 96 per cent with a mean survival time of 4.1 years. Surgical sympathectomy alters the 3 year rate to 24 per cent and the 10 year rate to 50 per cent with a mean survival time of 6.1 years for the deceased.

TABLE I.

MORTALITY RATES AT FOUR YEARS OF PATIENTS SUBJECTED TO SURGICAL SYMPATHECTOMY USUAL MEDICAL MEASURES AND CHEMOTHERAPY (PER CENT)

| Smithwick Group | Smithwick's Series (420)
Ages 38-47 | | White's Series (421)
Ages 30-60 | | Author's Series
Ages 34-76
Chemotherapy | |
|-----------------|--|----------|------------------------------------|----------|---|-----------|
| | Medical | Surgical | Medical | Surgical | Stopped | Continued |
| I | 10 | 3 | | | — | 0 |
| II | 33 | 12 | | | 32 | 1 |
| III | 88 | 19 | 81 | 24 | 38 | 3 |
| IV | 87 | 52 | | | 100 | 20 |
| Azotemia | (100) | † | (100) | † | 100 | 45 |

* Most patients were 40-60

† Not suitable for operation because of high operative mortality

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|-------------------------|--|----------|--------------------------------------|----------|--|----------------|
| | Medical | Surgical | Medical | Surgical | Stopped | Con-
tinued |
| I | 10 | 3 | | | — | 0 |
| II | 33 | 12 | | | 32 | 1 |
| III | 58 | 19 | 84 | 24 | 38 | 3 |
| IV | 87 | 52 | | | 100 | 20 |
| Azotemia | (100) | † | (100) | † | 100 | 45 |

* Most patients were 40-60

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Chapter IX

A PRELIMINARY APPROACH TO THE TREATMENT OF ATHEROSCLEROSIS

OBVIOUSLY, control of a patient's hypertension will do no more than relieve cardiac strain prevent further nephrosclerosis prevent cerebral hemorrhage and relieve angina pectoris. Theoretically it will slow that part of the rate of progression of atherosclerosis which is dependant upon an elevated blood pressure. Since atherosclerosis is probably reversible (443) at least in so far as cholesterol-containing plaques are concerned (and possibly calcification (422)) treatment of the whole patient and his diseases becomes essential for prolongation of a life potentially shortened by cardiovascular damage. Therefore an outline of the method we have used is given here. The method involves practical measures based on theoretical approaches of most promise. Since it is most difficult to measure alterations in this disorder for the better or worse until massive accidents occur only time will tell if the results are favorable.

The serial measurement of lipoprotein fractions in blood is a procedure confined to the larger specialized centers. Total plasma cholesterol however is readily measured in most hospital laboratories. Based upon the assumption that lowered plasma cholesterol will in part prevent deposition of esters in plaques one can attempt to lower these values by using some of the influences discussed in Chapter VII.

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in the kind of fat in the American and European diet. From 30 to 40 per cent of the caloric intake comes from fat mainly of animal origin. The purpose of the diet therefore is to restrict animal fat and hydrogenated vegetable oils and to provide an adequate intake of unsaturated vegetable fats containing linolenic acid. The basic rules are

- A No obvious fat of animal origin should be eaten. Modern methods of fattening cattle for slaughter make a saturated body fat.
- B No hydrogenated vegetable oils should be used since hydrogenation saturates an unsaturated fatty acid (Table LI).
- C Natural fat of vegetable origin containing the higher unsaturated fatty acids can be eaten in amounts as large as practicable since these contain the essential unsaturated fatty acids linolenic and linoleic.
- D In general reduce the fat content of the diet to about 20 per cent of the caloric intake.

The most available sources of essential fatty acids are in soy bean and corn oil with the following iodine numbers

| | Iodine No | Remarks |
|----------------|-----------|--------------------------|
| Soy bean oil | 130 | Contains 11% linolenate |
| Corn oil | 115 | Contains 0.5% linolenate |
| Cottonseed oil | 105 | Contains no linolenate |
| Sesame oil | 103 | Contains no linolenate |
| Peanut oil | 85 | Atherogenic in animals |

In order to obtain enough protein without animal fats the following are recommended

All kinds of fish and shellfish. Fish oils have a high iodine number.

Poultry and game avoiding the fat (except domestic goose and duck). Chicken fat is high in linoleate.

Lean beef, lamb and veal. Most animal fat is low in

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TABLE LII

CHANGE IN PLASMA CHOLESTEROL WITH ORAL EDTA (5.0 Gm /DAY)

| Patient | Sex | Age | Control
(mg %) | Chs 20
(mg %) | Interval
(weeks) | Major Diagnosis |
|---------|-----|-----|-------------------|------------------|---------------------|----------------------------------|
| W. H. | ♂ | 54 | 293 | -154 | 20 | Angina pectoris |
| B. McD. | ♂ | 54 | 278 | -150 | 35 | Peripheral vascular disease |
| I. S. | ♀ | 40 | 276 | -40 | 4 | Arterial hypertension |
| E. B. | ♂ | 63 | 253 | -58 | 16 | Coronary occlusion, convalescent |
| G. H. | ♂ | 45 | 252 | -36 | 23 | Angina pectoris |
| M. S. | ♀ | 49 | 237 | -37 | 14 | Arterial hypertension |
| E. S. | ♂ | 77 | 223 | -74 | 3 | Arterial hypertension |
| E. S. | ♂ | 48 | 210 | +18 | 44 | Angina pectoris |
| H. D. | ♂ | 63 | 189 | -49 | 8 | Angina pectoris |
| R. S. | ♂ | 54 | 177 | -38 | 12 | Angina pectoris |
| J. B. | ♀ | 59 | 178 | +16 | 4 | Arterial hypertension |
| Mean | | | 233 | -55 | | |

vessels and symptoms or signs are present the method of Clarke, Clarke and Mosher for removing metastatic calcium may be used (422). Trisodium EDTA, 5.0 Gm in 500 ml 5 per cent glucose solution is slowly infused intravenously over 2 to 6 hours. The patient is taught to slow the infusion at the appearance of unusual symptoms. Strangely enough hypocalcemic tetany does not appear under these precautions. Ionized calcium salts and calcium chelated to proteins and peptides at a weaker stability constant than 10.6 ($\log K_2$ EDTA) are probably removed; the strongly chelated calcium in bone is probably not.

An injection is given daily for 5 days; 2 days are allowed for rest and the 5-day course repeated. After a month or more for evaluation of symptoms a second 5.0 Gm is administered.

RESULTS EXPECTED

In Table LII are shown changes in blood cholesterol levels using calcium disodium ethylenediamine tetraacetate (Calcium Versenate) in doses of 1.0 Gm per day. In Table LIII are shown the changes produced by this agent

TABLE LII

CHANGE IN PLASMA CHOLESTEROL WITH ORAL EDTA (1.0 GM /DAY)

| Patient | Sex | Age | Control
(mg %) | Change
(mg %) | Interval
(weeks) | Major Diagnosis |
|---------|-----|-----|-------------------|------------------|---------------------|----------------------------------|
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| I. S. | ♀ | 10 | 276 | - 60 | 4 | Arterial hypertension |
| E. B. | ♂ | 62 | 253 | - 58 | 16 | Coronary occlusion, convalescent |
| G. H. | ♂ | 45 | 252 | - 36 | 25 | Angina pectoris |
| G. S. | ♀ | 49 | 251 | - 37 | 14 | Arterial hypertension |
| E. S. | ♂ | 77 | 225 | - 74 | 3 | Arterial hypertension |
| E. S. | ♂ | 48 | 210 | + 18 | 44 | Angina pectoris |
| H. D. | ♂ | 33 | 189 | - 49 | 8 | Angina pectoris |
| R. S. | ♂ | 54 | 177 | - 38 | 12 | Angina pectoris |
| J. B. | ♀ | 30 | 178 | + 16 | 4 | Arterial hypertension |
| Mean | | | 233 | - 55 | | |

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An injection is given daily for 5 days. 2 days are allowed for rest and the 5-day course repeated. After a month or more for evaluation of symptoms a second 50 Gm is administered.

RESULTS EXPECTED

In Table LII are shown changes in blood cholesterol levels using calcium disodium ethylenediamine tetraacetate (Calcium Versenate) in doses of 1.0 Gm per day. In Table LIII are shown the changes produced by this agent

with diet and vitamin B₆ added. In general the cholesterol changes are downward although in some cases they are resistant to all three forms of therapy. Some depressed values did not rise when EDTA was discontinued, an expected result if trace metals were being removed.

All patients with angina pectoris were relieved of attacks of pain either completely or partly in that they occurred less than once a month. No electrocardiographic changes in the direction of normal were observed. No signs of hepatocellular damage developed.

Comment. While untried for periods long enough to evaluate these results on the disease, there is little doubt that cholesterol values can become quite low by this form of treatment. Changes in the degree of atherosclerosis are difficult to measure, but rough estimates of improvement in the disease can be estimated, especially when it has advanced far enough to give local ischemic symptoms. In the coronary arteries, relief of angina pectoris if it is real and not imaginary suggests resorption of plaques. In the aorta, lessening of the widened pulse pressure suggests a return of aortic elasticity. In the legs, relief of claudication indicates improvement in blood flow. In the cerebral area, abolition of minor paraesthesias and paralytic episodes indicates reabsorption of plaques. Some changes may be expected in time except for a return of aortic elasticity.

Therefore, if degenerative cardiovascular disease is to be treated as in the past, —

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Therefore, if degenerative cardiovascular disease is to be treated as mentioned, the health of the

manifestations include emotional tension anxiety, excessive drive nervousness and the diencephalic blush. The blush is induced by histamine and resembles that seen with excessive quantities of circulating serotonin. Tension nervousness anxiety result in some individuals from epinephrine isoamylamine tyramine and those synthetic or natural methylated analogues which inhibit cerebral monamine oxidase (ephedrine amphetamine etc.) thus preventing oxidative deamination of naturally occurring substances.

From the huge amounts of tranquilizers sold the American public one might believe that chemically mediated nervous disorders were almost a national disorder. That many individuals might be so affected could be inferred from the abnormal trace metal content of American tissues if one interfered with vanadium or monamine oxidase or there was deficiency of vanadium. Primary amines could be implicated as causes of a widespread cerebral disorder.

Hereditary The ability to react to stress by vasospasm is an hereditary trait apparently transmitted as a Mendelian dominant.

Neurogenic The sympathetic nervous system is over active most likely because of increased cortico-hypothalamic activity. The posterior hypothalamus for which serotonin has a predilection is apparently stimulated more than is the anterior the chemical mediator of which is not known. Cortico-hypothalamic activity is increased as a result of somatically formed primary amines. Neurogenic vasospasm causes neurogenic renal ischemia.

Renal Renal disturbances dependent upon ischemia produce humoral vasoconstrictor substances. Trace metals both normal and abnormal are involved. Two metabolic pathways may be considered.

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II Renin is released possibly because of the acidity secondary to the lessened formation of ammonia (renin is extracted from kidney only at acid pH) This postulate is unproven and not too sound but we have no better one Renin comes from the superficial areas of the cortex of the kidney which becomes markedly acid when the renal artery is constricted Adjustments take place with time—several weeks

Result

- a) Hypertensin (angiotonin) is formed in blood at first through the physical release of renin (found)
- b) With time renin itself is no longer released into blood but continues to act *in situ* (not proven but renin disappears from blood) Perhaps renin is slowly modified into a somewhat different proteolytic enzyme
- c) Hypertensin I or its analogue formed in kidney is active on blood vessels becomes activated either 1) through decarboxylation leaving an active terminal NH_2 , the decarboxylase being in blood and kidney or 2) through action of a specific peptidase splitting off one or two amino acids and leaving a terminal $-\text{NH}_2$. In this latter event the peptidase would necessarily be a manganous enzyme The second pathway is the more logical one as peptidases are known and peptide decarboxylases are not Ordinarily in the absence of renal ischemia the small amounts of renin released into the renal venous blood form hypertensin which is inactivated both in kidney and in blood In renal ischemia the shift of locus of catabolism of hypertensin is from kidney to peripheral vasculature (theoretical but monamine oxidase acts on both hypertensin and pherentasin both peptides and it probably occurs in smooth muscle of blood vessels)

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The net results would be cortical acidity less urinary ammonia and sodium wastage, the same as those found in organic renal ischemia but appearing by somewhat different routes. Primary amines in blood however would not be elevated (Fig 38)

{ If cortical acidity is the stimulus for the action of renin, hypertensin I would be formed *in situ* and released into renal venous blood where it would be converted to hypertensin II (phorontasin) by action of a specific manganous peptidase. Thus both organic renal ischemia and cadmium can cause the same end results. Naturally renal ischemia accompanying neurogenic or phorontasin vasoconstriction would call into action pathway I

Therefore trace metals can be involved in the hypothetical peptidase probably manganous which converts hypertensin I to hypertensin II, in monamine oxidase which inactivates it, in the decarboxylases and amine oxidases which are concerned in the hypertensive state and even in tyrosinase (copper) which can inactivate norepinephrine, epinephrine, hydroxytyramine and tyramine)

Therapeutic Note: Drugs or procedures which block sympathetic nerve impulses will counteract only the neurogenic portion of hypertension. Drugs or procedures which a) act to dilate vascular smooth muscle, b) increase renal plasma flow, or c) inactivate hypertensin II or phorontasin, will counteract the nephrogenic portion of hypertension. All known inactivators are metal binding or chelating agents.

The actions of hydralazine are fourfold

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The actions of hydralazine are fourfold. ✓

1 Decarboxylase inhibition with the result that renal amino acid metabolism is further suppressed and therefore less primary amine is formed

2 Monamine oxidase stimulation with the result that those primary amines which are formed are oxidized more readily These include pherentasin or hypertensin II

3 Hypertensin and pherentasin are both directly inactivated either through carbonyl linkage or what is more probable removal of a chelated trace metal necessary for the integrity of the peptides

4 Constricted vascular smooth muscle is dilated no matter what causes the constriction by some unknown process which could be dependent either upon carbonyl or sulphhydryl binding or upon metal chelation

In addition histaminase is inhibited a reaction common to many hydrazides

Adrenocortical Renal sodium wastage (or need as in heart failure) probably causes adrenal cortical production of aldosterone (theoretical but logical) This steroid probably sensitizes blood vessels to circulating vasoactive amines and sympathetic discharges through intracellular sodium potassium alterations (proven only for DOCA) Most cases of hypertension exhibit secondary aldosteronism because of renal sodium wastage

Primary aldosteronism by sensitizing vascular smooth muscle to normally circulating vasoactive amines and normal sympathetic tone can produce a moderate degree of hypertension with normal renal plasma flow Cases of this nature are not unusual This type of hypertension while benign can slowly develop into a more serious variety with congestive heart failure the usual end result

Therapeutic Note While dietary salt restriction may induce enough sodium loss to negate the sensitizing effect of cortical steroids and salt on blood vessels it stimulates

1 Decarboxylase inhibition with the result that renal amino acid metabolism is further suppressed and therefore less primary amine is formed

2 Monamine oxidase stimulation with the result that those primary amines which are formed are oxidized more readily These include pherentasin or hypertensin II

3 Hypertensin and pherentasin are both directly inactivated either through carbonyl linkage or what is more probable removal of a chelated trace metal necessary for the integrity of the peptides

4 Constricted vascular smooth muscle is dilated no matter what causes the constriction by some unknown process which could be dependent either upon carbonyl or sulphhydryl binding or upon metal chelation

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② Cholesterol has a predilection for making unsaturated fatty acid esters. When insufficient unsaturated fatty acids are available for esterification saturated fatty acids are used. These esters are quite insoluble and probably have lower specific gravities. Possibly breakdown metabolism or excretion of cholesterol is more easily accomplished when esters are unsaturated than when made of saturated long chain fatty acids.

These two ideas are highly speculative. The mechanism of lowering plasma cholesterol by essential fatty acids is not understood.

Factors which may influence the deposition of cholesterol esters in sub-intimal spaces are

C Physical—Intra arterial pressure and changes of pressure (turbulence) at bifurcations of major vessels (Found)

D Metabolic—Pyridoxal deficiency causes sub-intimal lesions identical microscopically to pre-atherosclerotic lesions observed in animals and man (Found)

a) Pyridoxal is necessary for the integrity of the mucopolysaccharides of sub-intimal ground substance (Inferred)

b) Pyridoxal affects fatty acid metabolism by promoting the synthesis of essential fatty acids from less unsaturated ones (Found)

c) Experimental pyridoxal deficiency and essential acid deficiency are quite similar in signs differing only in a few basic enzymatic disturbances (Found). Vitamin B₆ will partly relieve essential fatty acid deficiency; essential fatty acids will partly relieve vitamin B₆ deficiency.

The biochemical interrelationships of three of these influences are

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application of therapy present and to come Rapid improvements are expected

① Reduce blood pressure of hypertensive patients to a mean level of 140/90 mm Hg (or as low as tolerable) and keep it there indefinitely Two drugs are usually necessary given frequently regularly and carefully one should act on nerves and the other on vascular smooth muscle

② Lower plasma cholesterol to 120 to 160 mg per 100 ml (or about the same levels in mg per cent as systolic pressure is in mm Hg) This can be accomplished slowly in some individuals and soon will be in most by

a) Metal chelation probably removing from liver an abnormal trace metal affecting synthesis Chelation and removal of metastatic calcium in blood vessels can probably be accomplished when desirable

b) Diet based on Less total fat to about 20 per cent of caloric intake Less animal fat especially saturated fatty acids General dairy products and pork are avoided Adequate ascorbic acid (probably 0.5 Gm per day)

c) Vitamin B₁₂ adequate This coenzyme is given for logical but untested reasons

It is a long step from a lowered cholesterol to absorption of plaques but the assumption is reasonable

There are enough ideas now under experimental observation to strengthen the belief that atherosclerosis is a reversible disease at least in so far as the fatty and calcific deposits are concerned Arterial hypertension in man can be controlled indefinitely and sometimes reversed Application of therapy to both diseases in the same individual may be expected to reverse in part the lethal and disabling effects of each

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INDEX

A

- α*-globulins 59 76-77
 - from beef 76
 - from dogs 76
 - from horses, 16
 - in liver 88
- Abdominal
 - worms 244
 - lymphosarcoma 61
 - scars 257
- Abnormal
 - hair in cattle 175
 - trace metals in man 116-185 206
- Abraham J 311
- Abrams M L 314
- Abreu B E 302
- Absence of kidneys 60
- Acetate 8, 9° 208 224 225 292 294
- Acetal lipid 221
- Acetaldehyde 8, 92
- Acetic acid 221
- Acetoacetic acid, 224
- Acetonyl mercaptan 99
- Acetyl acetone 1 8
- Acetylamine 162
- Acetyl choline (quaternary ammonium compound) 40-41
- Aching 257
- Achor R W P 302
- Acid
 - content in urine 59 236, 238
 - esters of cholesterol 217
 - foods 198
 - renal cortex, 58-59
- Ackerman N W 299
- Acridavine 164
- ACTH 164
- Actomyosin 149
- Acute infections 70 183
- Acute nephritis 10
- Actions of adrenergic blocking agents in man table on 48
- Actomyosin 234
- Acute vasospastic states 77
- Acyl Co-enzyme A dehydrogenase 147 148 230
 - copper flavinoid in 147
- Adams E 316
- Addison's disease 134 136
- Adenoma in adrenal cortex 11
- Adipoin 165
- Adipose tissue trace metals in estimate of 170-171
- Adrenalin 157
- Adrenals 4 6-7 11 40 49-50 109-110 125 132 140 170-171 116-185 194 196-197 199 224 241 243 276 286 291 292
 - aluminum in 176-183
 - barium in 180
 - cadmium in 196
 - cholesterol in 221
 - cortex 11 49-50 109-110 125 132 140 213 276 291 292
 - adenoma in 11
 - in hypertension 138
 - overactivity of 139
 - relation of to medulla 133-135
 - hyperfunction 276
 - mechanisms 132 140
 - clinical findings of 135
 - steroids 133-134

INDEX

A

- α -globulins 29 76-77
 - from beef 76
 - from boga 76
 - from horses, 16
 - in liver ■
- Abdominal
 - scars 244
 - lymphosarcoma 61
 - scars 257
- Abnormal
 - hair in cattle 173
 - trace metals in man 116-183 206
- Abraham J 311
- Abrams M L 314
- Abreu B E. 302
- Absence of kidneys 60
- Acetate 8, 9° 206 224 225 292
 - 294
- Acetal lipid 221
- Acetaldehyde 8, 92
- Acetic acid 221
- Acetoacetic acid, 224
- Acetonyl mercaptan 99
- Acetyl acetone 1 8
- Acetyl amino 162
- Acetyl choline (quaternary ammonium compound) 40-41
- Aching 257
- Achor R W P 302
- Acid
 - content in urine IV 236, 283
 - esters of cholesterol 217
 - foods 198
 - renal cortex, 58-59
- Ackerman N W 299
- Acridavine 161
- ACTH 164
- Actomyonin 149
- Acute infections 70 183
- Acute nephritis 10
- Actions of adrenergic blocking agents in man table on 48
- Actomyonin 234
- Acute vasospastic states 77
- Acyl Co-enzyme A dehydrogenase 147 148 230
 - copper flavinoid in 147
- Adams E. 318
- Addison's disease 134 136
- Adenoma in adrenal cortex 11
- Adipoin 165
- Adipose tissue trace metals in
 - summary of 170-171
- Adrenalin 157
- Adrenals 4 6-7 11 40 49-50 109-110 125 132 140 170-171 176 183 194 196-197 199 224 241 243 276 286 291 292
 - aluminum in 176-183
 - barium in 180
 - cadmium in 196
 - cholesterol in 224
 - cortex 11 49-50 109-110 125 132 140 213 276 291 292
 - adenoma in 11
 - in hypertension 138
 - overactivity of 139
 - relation of to medulla 133-135
 - hyperfunction 276
 - mechanisms 132 140
 - clinical findings of 135
 - steroids 133-134

- Amine oxidase—see Monamine oxidase
 Amino acids 31 37 360 372 74
 7 83 9 94 99 110 170 192
 123 143 151 161 162 167 187
 188 193 197 208 221 285 290
 decarboxylation of 64 140 209
 by kidney 64
 deamination of 31 37 79 87 12
 4 94 110 188
 theory of 72 72
 in vasoactive peptides chart on
 76
 metabolism 67 226
 renal tubular reabsorption of 193
 Aminoaciduria cadmium 193 249
 Amino- α -mercaptobenzothiazole 99
 Amino grouping (primary secondary tertiary cyclic tertiary) 149
 Aminoguanidine HCO_2 87 97
 Aminopeptidase 197
 Aminopterin 161 167 187
 Aminothiazole 162
 Ammonia 97 103 135 153 155
 88-89
 in urine 288-89
 Ammoniated mercury freeble cream
 action of 153
 Ammonium
 chloride 97
 compounds 135
 nitrogen 103
 Amphetamine (Benzedrine) 51 63
 233
 Anhydrous 219 231 270
 Androgens 133
 Androgenic overproduction 138
 Anaerobic decarboxylation 37 38
 -0 62 266
 Anesthetics 222 92-109
 effect of intravenous sulphydryl
 compounds on the diastolic
 pressures of 98
 effect of intravenous EDTA on
 diastolic blood pressure of
 96-109
 Anesthesia peripheral vasoconstrictor
 under 38
 Analgesic agents 146-162
 Analysis of metals 163
 some reagents for 163
 Anaphylactic shock 166
 Anatomical causes of renal ischemia
 76-82
 Anatomic chemistry of phospholipids
 234
 Anderson J T. 323 325
 Andrus S B 371
 Anemia 99 117 164 174 175
 aplastic 164
 hypochromic 170
 in infancy 173
 Anercyrisms 237
 Angina pectoris 201 233 277 278
 279 281 283
 syndrome 203
 Angiotensin (constrictor peptide)
 58 64-67 69 71 72 110
 Animals
 atherosclerosis in 230
 ataxic 170
 blood protein obtained from
 273
 fat 233 278-279 290
 tissues
 aluminum in 191
 nickel in 190
 Anionic elements 151
 Anticholin A 320
 Ankle edema 231
 Anorexia 173 175
 Anolysen (pentolamine) 43
 Antiautonal hormones 140
 Antibiotics 63 167 161 21, 261
 bacterial resistance to 44
 Antithrombotic 73
 Antidiuretic properties 72
 Antineoplastic action 35

- Amine oxidase—see Monamine oxidase
- Amino acids 31 37 368 67 72 74
 11 87 9 91 99 110 100 152
 113-114 151 161 162 167 167
 102 101 197 206 221 285-290
 decarboxylation of 64 100 201
 by kidney 64
 decarboxylation of 31 37 79 67 12
 4 94 110 188
 theory of 12 12
 in vasoactive peptides chart on
 96
 metabolism 67 224
 renal tubular reabsorption of 193
- Aminoaciduria cadmium 193 249
- Amino- α -mercaptobenzoic acid 99
- Amino grouping (primary secondary tertiary cyclic tertiary) 149
- Aminoguanidine HCO_2 87 97
- Aminopeptidase 197
- Aminopyrine 161 167 187
- Aminothiazole 162
- Ammonia 97 103 135 153 155
 285-289
 in urine 288-289
- Ammoniated mercury freckle cream
 action of 153
- Ammonium
 chloride 97
 compounds 135
 nitrogen 103
- Amphetamine (Benzedrine) 51 63
 283
- Antyloids 219 231 270
- Androgens 135
- Androgenic overproduction 138
- Anaerobic decarboxylation 37 111
 10 62 206
- Anesthetics 224 92-100
 effect of intravenous sulphydryl
 compounds on the diastolic
 pressure of 98
 effect of intravenous EDTA on
 diastolic blood pressure of
 96-109
- Anesthesia peripheral vasoconstrictor
 under 111
- Analgesic agents 146-162
- Analysis of metals 163
 some reagents for 163
- Anaphylactic shock 166
- Anatomical causes of renal ischemia
 78-82
- Anatomic chemistry of phospholipids
 234
- Anderson J T. 3.3 323
- Andrus S B 371
- Anemia 93 117 164 174 175
 aplastic 164
 hypochromic 170
 in infancy 173
 incursions 237
- Angina pectoris 201 213 273 274
 275 277 281 285
 syndrome 204
- Angiotensin (constrictor peptide)
 58 64-67 69 71 72 110
- Animals
 atherosclerosis in 230
 ataxic 175
 blood protein obtained from
 273
 fat 233 278-279 295
 tissues
 aluminum in 191
 nickel in 190
- Anionic elements 151
- Anthrax 11 320
- Ankle edema 231
- Anorexia 173 175
- Anolysis (pentolism) 43
- Antisecretory hormones 110
- Antibiotics 63 107 161 217 264
 bacterial resistance to 47
- Anticoagulant 73
- Antidiuretic properties 72
- Antineoplastic action 35

- Atherosclerotic ultra-centrifugal lipoproteins 36
Atherosclerosis 152 190 202 213-214
24 013
cholesterol-filled 152
of the renal artery 242 043
Atherosclerosis 19 94 112 113 200 251
Atherosclerosis (Warte Strumpell) 231
thrombotic 19
Atkinson U. H. 212 216 21 21
Atchell L. 211 201
Atwood Vanadium in 187
Asparagine 61
Aspartic acid 63 71 16 038
Aspergillus niger metal to 180
Asaume 151
Aschme 20
Aschme 20
Asymptomatic duodenal obstruction 8 20 210
Asystolic arterial pressure gradients (examples) 14
Auer 51 110
in animals 110
Atherosclerosis
abnormal trace metals as contributing cause of 192
among highland nomads 209
bilateral renal 61
cadmium as contributing cause of 192
case history of 9-10
cerebral 210
chromium as contributing cause of 190
clinical implications of 236-237
copper 235 030
effect of sex in 235 038
clearing factor of 236
etiological factors of 20
experimental results in treatment of 231 263
gangrene in 000
in animals 280
in China 13 203 210
dogs 200
rabbits 210
rats 200 210
in the aorta 185 210 235-236 201
lead as contributing cause of 190 191
lesions of 206 237
mechanisms in 203-237
method of treatment of 208 261
more frequent than hypertension 211
occlusion of the renal artery 60
pathogenetic factors in 000 260
preliminary approach to the treatment of 277 263
renal 218
some common denominators of hypertension and 208 211
summary on 200 206
in as contributing cause of 192
vitamin B₆ and 207 257
Western civilization and 205
Atherosclerotic plaques 90 127
ATPase 149 150
Ascorbic acid 221
Atropine 110
Aureomycin 157
Aminocaproic acid 200
Auscultation 270
Autonephrectomy 82
Autonomic blocking agents 41 42
3 265
Autonomic nerves 4
Autopsies 78 11 20 13 20 169
179 180 203-204 211
sclerosis at 203
Auge sodium 84 191
Aude 81 100
Anemia 10 16 19 52 53 60-61
81 110 23 211 214 2 3 25,
260-268 61-271 273-274
chart on progress in 273

- Atherogenic ultra-centrifugal lipoproteins 56
 Atherosclerosis 152 190 207 213-214 24 213
 cholesterol filled 152
 of the renal artery 242-243
 Anthrax 19 94 112 113 200 231
 Anthrax Marie Strumpell 231
 rheumatoid 19
 Aridus U. S. 212 216 21 21
 Arion L. 212 21
 Ascidia (Anadum) in 187
 Asparagae 61
 Aspartic acid 53 71 16 938
 Aspergillus niger metal in 180
 Ascaris 151
 Ascaris 20
 Ascaris 20
 Asymptomatic duodenal obstruction 8 20 210
 Asystolic arterial pressure gradients (examples) 14
 Azela 51 170
 in animals 170
 Atherosclerosis
 abnormal trace metals as contributing cause of 192
 among highland nomads 209
 bilateral renal 80
 cadmium as contributing cause of 132
 case history of 9-10
 cerebral 210
 chromium as contributing cause of 190
 clinical implications of 216-217
 coronary 213 930
 effect of sex in 213 936
 clearing factor of 210
 etiological factors of 20
 experimental results in treatment of 21 283
 gangrene in 200
 in animals 280
 in China 19 203 210
 dogs 200
 rabbits 210
 rats 200 210
 in the aorta 185 210 213-236 201
 lead as contributing cause of 190 191
 lesions of 206 237
 mechanisms in 203-237
 method of treatment of 208-281
 more frequent than hypertension 211
 occlusion of the renal artery 80
 pathogenetic factors in 200-208
 preliminary approach to the treatment of 277 283
 renal 218
 some common denominators of hypertension and 208 213
 summary on 200 206
 in as contributing cause of 192
 vitamin B₆ and 207 247
 Western civilization and 205
 Atherosclerotic plaques 20 127
 ATPase 149 150
 Atoropherol 221
 Atropine 110
 Aureomycin 152
 Aminoacetic acid 200
 Auscultation 270
 Autonephrectomy 82
 Autonomic blocking agent 41 43 3 287
 Autonomic nerves 4
 Autopsies 78 11 2, 13 20 169 174 180 203-21 213
 sclerosis at 203
 Aze sodium 81 150
 Azide 81 150
 Azidemia L. 16 19 52 53 60-61 81 110 23 211 214 2 3 25, 250-258 61-271 273-274
 chart on progress in 273

- Benodaine (Piperoxan) 49
 Benzene rings 49
 Benzedrine (Amphetamine) 31
 Benzodioxanes, 48-50 60
 Benzoin-oxime 163
 Benzyl 71
 Benzylamine derivatives of 43
 Benzylthiopseudourate hydrochloride 10ⁿ
 Bernhart F W 319
 Bernheim F. H 184 186 234 301 317
 Bernheim M L C., 184 186 234 317
 Bernier metal and 176
 Berry R. L. 300
 Bersworth F C 374
 Bertrand D 317
 Beryllium 144 150-151 159 167 180 200
 poisoning 200
 Beta globulin 240
 Betalipoproteins 236
 Beveridge J M R., 323
 Bhadrakom S 303
 Bibliography of the literature on the minor elements and their relation to plant and animal nutrition 316
 Bicarbonate 286
 Biehl J P 309
 Bifurcating arteries 79 203
 Bifurcation of the aorta 203
 Bilateral
 adrenalectomy 276
 hydronephrosis 61
 papilledema 270
 renal arteriolar sclerosis 8ⁿ
 renal arteriosclerosis 80
 Bioassay 244
 Biochem J 64
 Biochemical alterations in blood vessels 4
 Biophysics 81 178 231
 Bing R J 303
 Binger C. A 299
 Binion J 312
 Bis (diethylthiocarbamyl) disulfide (antabuse) 162
 Bismuth 151 153 161 164 167 179 185 199
 in the kidneys 199
 in the liver 199
 in the lungs 179
 in the skin 153
 Black M W., 310
 Blackman S S Jr 79-80 308
 Bladder 170-171 176 183 194 241
 trace metals in 170-171 176-183 194
 Blascho H 303
 Bleeding 251
 Blipoproteins 217 236
 Block 215
 Blocking actions
 autonomic 263
 clinical implications of 50-54
 in vivo 92
 on rabbit's arterial strip 92-93
 Blood cholesterol 211 217 223-228
 levels examples of in healthy male subjects 216A
 levels in man effect of various fats on 223-228
 Blood
 clotting of 15.
 dyscrasias 161
 flow femoral 48
 flow mesenteric 48
 flow renal 48 208
 lipids in 206 213 216
 necrotic calcareous in vessels 292
 normal cholesterol levels in chart on 212
 pressure
 depression of by drugs 30
 examples of adequate control of 255

- Benodaine (Piperoxan) 49
 Benzene rings 49
 Benzedrine (Amphetamine) 31
 Benzodioxanes, 48-50 60
 Benzoin-oxime 163
 Benzyl 71
 Benzylamine derivatives of 4,
 Benzylthiopseudourea hydrochloride 10ⁿ
 Bernhart E W 31ⁿ
 Bernheim F., 31 184 186 234 301 317
 Bernheim M L C., 184 186 234 317
 Bernhart metal and 176
 Berry R. L. 300
 Berworth F C 3ⁿ4
 Bertrand D 317
 Beryllium 144 150-151 159 167 180 200
 poisoning 200
 Beta globulin 2,0
 Beta lipoproteins 256
 Beveridge J M R., 323
 Bhadrakom S 303
 Bibliography of the literature on the minor elements and their relation to plant and animal nutrition 316
 Bicarbonate 236
 Biehl J P 309
 Bifurcating arteries 79 203
 Bifurcation of the aorta 203
 Bilateral
 adrenalectomy 276
 hydronephrosis 61
 papilledema 270
 renal arteriolar sclerosis 8ⁿ
 renal arteriosclerosis 80
 Bioassay 214
 Biochem J 64
 Biochemical alterations in blood vessels 4
 Biopyrics 81 1ⁿ8 231
 Bing R J 303
 Binger C. A 299
 Binson J 312
 Bis (diethylthiocarbamyl) disulfide (antabuse) 162
 Bismuth 151 153 161 164 167 179 185 199
 in the kidneys 199
 in the liver 199
 in the lungs 179
 in the skin 153
 Black M W., 310
 Blackman S S Jr 79-80 308
 Bladder 170-171 176 183 194 241
 trace metals in 1,0-171 1 0-183 194
 Blascho H 303
 Bleeding 251
 B-lipoproteins 217 256
 Block 215
 Blocking actions
 autonomic 263
 clinical implications of 50-54
 in vivo 92
 on rabbit's arterial strip 9ⁿ 93
 Blood cholesterol 211 217 223-228
 levels - examples of in healthy male subjects 216A
 levels in man effect of various fats on 223-228
 Blood
 clotting of 15,
 dyscrasias 161
 flow femoral 48
 flow mesenteric 43
 flow renal 48 208
 lipids in 206 213 216
 metastatic calcium in vessels 29,
 normal cholesterol levels in chart on 212
 pressure
 depression of by drugs 30
 examples of adequate control of 255

Burchard 21^a 216^a
 Bush R. D., 307
 Bush sickness in calf 1 4
 Butt E. M. 316
 Butter 173 223 225-226 278 290
 composition of 223
 Buttermilk 290
 Butyric dehydrogenase 299
 Buxton J. 307
 Bress S. O. 300
 Byron F. B. 303

C

C-carboxyl labeled acetate 187
 Cachexia 173
 Cadaverine 63
 Cadmium 97 9 107 103 123 170
 143 144 151 153 155 161 167
 173 176 181 183 191 197 199
 200 202 288 290 293
 as contributing cause of atherosclerosis 192
 as contributing cause of hypertension 192
 in a toxic metal 19
 in adrenal 196
 in aorta 196
 in brain 196
 in heart 196
 in intestine 196
 in kidneys 193 194 1 6 181 183
 196-197 193 290
 in liver 176-183 196
 in pancreas 176-183 196
 in spleen 196
 in stomach 196
 in tissues 183 196
 muscle 196
 in thyroid 176-183 196
 in urine 17 200
 in vegetables 198
 nephritis 9 183
 plated vessels 198
 poisoning 9, 196 198

ice trays as cause of 196
 Calcium 91 107 118 127 141 190
 153 232 290-291
 citrate chelate 155
 disodium ethylenediamine tetraacetate (Calcium Versenate)
 91 232 290-291
 in bone 281
 poisoning 281
 ion 118
 in calcium 293
 salts 187
 Calcium 44, 112 157 314 318
 Campden's A. 300
 Camphor 33
 Candy Metal in 193
 Canned soups 11 in 280
 Cannon R. B. 301
 Carbon (C, carbonyl) 83 97 91
 115 115-116 117 118 150 1 2
 162 164 197 199 223 288
 Carbon atoms 223
 Carbon dioxide 197
 Carbanide 162
 Carbazone 164
 Carbonated beverages cadmium in
 19, 199
 Carbonic anhydrase 94 147 148 150
 1, 2 288
 Carbonyl binding 113
 Carbonyl linkage 291
 Carbonyl reagent 85 92
 Carboxypeptidase 71 118
 Carcinoma of prostate 278, 279
 Cass B. 318
 Cardiovascular disease 9-15 20
 49 48 57 110, 111 125 141 207
 210 216 219 233 26, 210-271
 27 27, 234
 and trace metals 141 202
 as inherited trait 20
 decompensation 263
 enlargement 10
 failure 175

Burchard 21^o 2163
 Bush R. D., 3^o
 Bush sickness in cattle 1 4
 Butt E. M. 316
 Butter 173 223 225-226 2^o 2^o 2^o
 composition of 2^o
 Buttermilk 2^o
 Butyric dehydrogenase 2^o
 Buxton J. 3^o
 Bress S. O. 3^o
 Byron F. B. 303

C

C¹⁴-carboxyl-labeled acetate 183
 Cachexia 173
 Cadaverine 63
 Cadmium 9^o 9 107 1^o 12^o 1^o
 145 141 151 153 155 161 167
 1^o 176 181 183 191 197 199
 200 20^o 288 290 293
 as contributing cause of atherosclerosis 192
 as contributing cause of hypertension 19_o
 ■ a toxic metal 19
 in adrenal 196
 in aorta 196
 in brain 196
 in heart 196
 in intestine 196
 in kidneys 1^o 1^o 1^o 1^o 181 183
 196-197 193 290
 in liver 176-181 196
 in pancreas 176-183 196
 in spleen 196
 in stomach 196
 in tissues 183 196
 muscle 196
 in thyroid 176-183 196
 in urine 1^o 200
 in vegetables 198
 nephritis 9 163
 plated vessels 198
 poisoning 9_o 196 198

100 trays as cause of 136
 Calcium 91 107 118 127 141 150
 15_o 232 240-241
 citrate chelate 155
 disodium ethylenediamine tetraacetate (Calcium Versenate)
 91 252 260-261
 in bone 281
 ionized 281
 ion 118
 in causative 293
 salts 107
 Calcium 4^o, 142 157 314 318
 Campbell K. V., 300
 Camphor 53
 Candy metal in 193
 Canned soups 1^o in 280
 Cannon R. B. 301
 Carbon (C¹⁴ carbonyl) 8_o 9_o 91
 115 145-146 147 148 150 1^o 2
 162 164 197 199 223 288
 Carbon atoms 223
 Carbon dioxide 197
 Carbamide 162
 Carbazone 164
 Carbonated beverages cadmium in
 19, 199
 Carbonic anhydrase 94 147 148 150
 1^o 288
 Carbonyl binding 113
 Carbonyl linkage 291
 Carbonyl reagent 84 92
 Carboxypeptidase 71 148
 Carcinoma of prostate 228-229
 Carr R. V., 318
 Cardiovascular disease , 9-13 20
 4^o 48 57 110-111 125 141 20^o
 210 216 249 253 26_o 210-271
 27 27_o 294
 no trace metals 141 202
 as inherited trait 20
 decompensation 26_o
 enlargement 10
 failure 175

Burchard 317 2381
 Bush & D 371
 Bush sickness in cattle 271
 Butt & V 316
 Butter 115 203 225 226 278 280
 combustion of 225
 Bu verius 280
 Butyric dehydrogenase 203
 Duxon J 302
 Evans S D 370
 Eyring T B 30

G

Gamma-carboxyl labeled acetate 189
 Lachaux L2
 Ladizesky 63
 Cadaverin 91 93 102 103 1 130
 113 144 151 153 155 161 167
 173 176 181 184 190 197 199
 200 202 284 290 293
 as contributing cause of atherosclerosis 104
 as contributing cause of diabetes 104
 as a toxic metal 104
 in adrenal 196
 in aorta 196
 in brain 196
 in heart 196
 in intestine 196
 in kidneys 153 155 176 181 183
 196 202 291 293
 in liver 153 183 196
 in pancreas 153 183 196
 in spleen 196
 in stomach 196
 in tissues 183 196
 muscle 196
 in thyroid 153 183 196
 in urine 196 200
 in vegetables 196
 nephritis 91 163
 platelets 196
 poisoning, 91 196 200

as cause of Y6
 Calcium 91 107 118 127 131 150
 151 252 293 291
 organic salts 153
 diiodine ethylenediamine 153
 case (Calcium lactate)
 91 2 2 293 291
 in bone 281
 ionized 281
 ions 153
 metastatic 281
 salts 107
 Calcium 11 110 1 7 314 318
 Campbell A 300
 Camphor 33
 Candy metal in 199
 Canned sugar 11 in 200
 Cannon W B 301
 Carbon (C¹⁴ carbonyl) 8, 92 94
 115 113-144 147 148 150 197
 167 161 197 199 203 288
 Carbon atoms 223
 Carbon dioxide 197
 Carbazole 162
 Carbazone 164
 Carbonated beverages cadaverin 10
 197 199
 Carbonic anhydrase 91 147 149 150
 153 289
 Carbonic binding 113
 Carbonyl linkage 291
 Carbonyl reagent 8, 92
 Carboxypeptidase 71 143
 Carcinoma of prostate 153 150
 Card B 7 318
 Cardiovascular disease 7 913 20
 41 18 27 110-111 121 141 202
 210 216 219 253 261 270 271
 273 277 291
 and trace metals 141 202
 as inherited trait 20
 decompensation 26,
 enlargement 10
 failure, 1 5

Burchard 171 2161
 Bush R. D. 371
 Bush sickness in cattle 271
 Buti E. V. 316
 Butter 119 223 225 226 278 230
 composition of 225
 Bu termite 280
 Butyric dehydrogenase 221
 Dutton J. 302
 Evans S. D. 370
 Dyrco F. B. 39

C

C-carboxyl labeled α case 189
 Cactus 112
 Cadaver 163
 Calcium 91 92 107 103 1 130
 113 114 131 153 123 161 167
 173 176 181 184 191 197 199
 200 201 284 290 293
 ■ contributing cause of stheror
 1 1014 1014
 ■ contributing cause of diabetes
 101 101 101
 ■ a toxic metal 101
 in adrenal 196
 in aorta 196
 in brain 196
 in heart 196
 in intestine 196
 in kidneys 173 151 176 181 183
 196 201 197 203
 in liver 176 183 196
 in pancreas 176 183 196
 in spleen 196
 in stomach 196
 in tissues 183 196
 muscle 196
 in thyroid 176 183 196
 in urine 191 200
 in vegetables 196
 nephritis 91 163
 plate 1 view 196
 poisoning 95 196 199

■ cause of 196
 Calcium 91 107 118 127 131 150
 151 252 203 281
 Cereals 163
 diuretic ethylethamine 101
 cause (Calcium Lactate)
 91 2 2 203 281
 in bone 281
 ionized 281
 ions 159
 metastatic 281
 salts 107

Cathin 11 110 1 7 516 216
 Campbell A. 1 100
 Camphor 53
 Candy metal 10 196
 Canned snuff 11 100
 Cannon W. B. 201
 Carbon (C¹⁴ carbon) 81 92 94
 113 113-114 147 148 150 197
 167 161 197 199 223 283
 Carbon atoms 223
 Carbon dioxide 197
 Carbazole 162
 Carbazone 161
 Carbonated beverages cadaver 10
 197 199
 Carbonic anhydrase 91 147 148 150
 151 280
 Carbonil binding 113
 Carbonil linkage 291
 Carbonil reagent 81 92
 Carboxypeptidase 71 141
 Carcinoma of prostate 152 150
 Cast B. Y. 316
 Cardiovascular disease 7 113 20
 41 11 57 110-111 121 141 202
 210 216 219 253 261 270 271
 271 277 291
 and trace metals 141 202
 ■ inherited trait 20
 decompensation 26,
 enlargement 10
 failure 1 3

- function of oxygen tension 64
- on substances with metal binding properties selectively affecting arterial hypertension 84
- Chorse 173 223 278 280
 dosage 280
 fat free % 80
- Chelons 170 131 234
- Chelating agents 83-91 95 103
 142-147 206 230 235 234 237
 251 238-239 291 292
- antiseptic, 157
- bactericidal 157
- drugs ■ 154-166
 examples of chart on 162 163
- fungal 157
- normal and abnormal metals in chart on 146
- Chelating compounds simple 1-4-155
- Chelation principles of 143-146
- Chemical structures of Yohimbine and Reserpine 248
- Chemical sympathectomy 275
- Chemosis 122 131 237
- Chemotherapy 275-276
- Chemosis 171 173
- Chickens 174 222 2 9
- Chicken fat, 279
- Child C. G., 298
- Children stillborn 121
- Chills, 34 188
- China atherosclerosis in 19 203 210
- China coronary thrombosis in 204
- China hypertension in 20 203
- Chloral hydrate 165
- Chloramphenicol, 162 164
- Chlorides 59 74 197 198
- Chlorides in water 197 198
- Chlorzondamine (Ecolid) 41 45 233 261
- Chlorophyll porphyrin of 147
- Chlorpromazine 34 35 51 164
- chart on incidence of side reactions and toxic effects in normotensive patients, 31 33
- effects of on system 35
- Chocolates 173 194
- Cholesterol 123 132 184 186 188-189 207 211 214 216-225 227 229 235 277 292 293 295
- aortic, 208
- digitonide 189
- esterified 216-223 233
 acid esters of 217
 ester nature of 218-223
- exogenous intestinal absorption of 221 222
- filled atheromata 132
- hepatic, 208
- in adrenal 224
- in arteries 209
- in blood 223 224
- in kidneys 128
- in liver 224
- in rats 207 224
- in serum 208 221
- lowering foods: essential fatty acid content of 227
- metabolism of 208 224
- phospholipid ratio 221
- plasma 210
- relation of to dietary fats 223-225
- synthesis by liver 188
- synthesis of from acetate 184
- synthesis possible pathway of chart on 224
- Cholesterylins 94
- Choline and ■ 93
- Choline esters, 41
- Choline oxidase 151 152 197
- Cholinergic drugs 52
 response to in injections 52
- Cholinergic stimulation 47
- Cholinesterase 92
- Chromatograms 77

- function of oxygen tension 64
 on substances with metal bonding properties selectively affecting arterial hypertension 84
 Chose 173 223 278 280
 cage 280
 fat free 280
 Choleas 170 131 231
 Chelating agents 83-91 95 103
 142-90° 206 230 231 234 237
 251 288-289 291 293
 antiseptic, 157
 bactericidal 157
 drugs as 153-166
 examples in chart on 162 163
 fungicidal 157
 normal and abnormal metals in chart on 146
 Chelating compounds simple 1-4-155
 Chelation principles of 143-146
 Chemical structures of Yohimbine and Reserpine 248
 Chemical sympathectomy 275
 Chemosis 120 131 232
 Chemotherapy 275-276
 Chiasmata 171 173
 Chickens 174 222 2 3
 Chicken fat, 279
 Child C. G., 298
 Children stillborn 121
 Chills, 34 188
 China atherosclerosis in 19 203 210
 China coronary thrombosis in 204
 China hypertension in 20 203
 Chloral hydrate 165
 Chloramphenicol, 162 164
 Chlorides 59 74 197 198
 Chlorides in water 197 198
 Chlorisondamine (Ecolid) 41 43 233 261
 Chlorophyll porphyrin of 147
 Chlorpromazine 34 35 51 164
 chart on incidence of side reactions and toxic effects in normotensive patients, 34 35
 effects of on system 35
 Chocolates 173 194
 Cholesterol 128 132 184 186 188-189 207 211 214 216-225 227 229 235 277 292 295 295
 aortic, 208
 digitonide 189
 esterified 216-223 235
 acid esters of 217
 ester nature of 215-223
 exogenous intestinal absorption of 221 222
 filled atheromata 132
 hepatic, 208
 in adrenal 224
 in arteries 209
 in blood 223 224
 in kidneys 128
 in liver 224
 in rats 207 224
 in serum 208 222
 lowering foods essential fatty acid content of 227
 metabolism of 208 224
 phospholipid ratio 221
 plasma 210
 relation of to dietary fat 223-225
 synthesis by liver 188
 synthesis of from acetate 184
 synthesis possible pathway of chart on 224
 Cholesterololysis 34
 Choline and 93
 Choline esters, 41
 Choline oxidase 151 152 197
 Cholinergic drugs 52
 response to in injections 52
 Cholinergic stimulation 47
 Cholinesterase 92
 Chromatograms 77

- Comment on adrenergic blocking agents 49-50
 Comment on antihypertensive drugs (tranquillizing drugs) 56-58
 Comment on hypertension 23
 Comment on secondary effects of hypertension 17
 Comparison of serum lipids cholesterol and lipid phosphorus in the old and new Yemenite immigrants in Israel 214
 Comparative doses of ganglionic blocking agents chart on 45
 Complex of factors in the human disease introduction 3-4
 Congenital malformations 213
 Congestive heart failure 63 70 73 199 243 244 250-251
 Conjunctivitis 94
 Conn H F 576
 Connell W F 323
 Constriction of renal artery 108
 Constrictor primary amines in the pulmonary circuit 68
 Convulsions 108 121 131
 Cook W J 318
 Cooper A R 318
 Copper 12 83 103 106 113 142 144 147 148 150-151 153 155 157 159 161 167 169 171 175 179 181 193 200-201 207 223 250 254 289
 binding agents 153
 catalyst 223
 chelates 104
 deficiency 172
 in cattle grazing pastures 175
 enzymes 103 148 193
 flavinoid in acyl-coenzyme A-dehydrogenase 147
 in hemoglobin formation 173
 in liver 181
 poisoning 173
 tyrosine 103
 Corticotin A C. 212 216A 304 310 313 350 321
 Corley R W. 302
 Corn 22, 226 279-280
 composition of 223
 oil 226 273
 Cornea vascularization of 175
 Corned beef 278
 Cornwell D G. 323
 Coronary atherosclerosis 213 235-236
 Coronary arterial disease 23 201 209-210 236 269
 Coronary arterial narrowing 238
 Coronary occlusion 3 9 240 243 273 281
 Coronary sclerosis 209-210
 Coronary thrombosis 23 201
 in Ho China 201
 Corrosion of hot water heaters 197
 Corrosive 11 53 136 157 164
 Costello R L. 317
 Cottage cheese 280
 Couper P T 303
 Cottonseed 22, 226 279
 composition of 223
 oil 226 279
 Cotton wool exudate 273
 Council on pharmacy and chemistry 303
 Cousins D B 312
 Cowdry E V 350
 Cows 23 226
 hypertension in 75
 Cox A J Jr 318
 Cortico-hypothalamic activity 283
 Cortex acidity of 59-59 289 290
 Cortex of the kidney 287
 Cortical steroids 291
 Cox C G 321
 Crema 278 280
 Credner A. 303
 Crisco hydrogenated oils in 227
 Crises treatment of 263-276

- Comment on adrenergic blocking agents 49-50
 Comment on antihypertensive drugs (tranquillizing drugs) 36-38
 Comment on hypertension 23
 Comment on secondary effects of hypertension 17
 Comparison of serum lipids cholesterol and lipid phosphorus in the old and new Yemenite immigrants in Israel 214
 Comparative doses of ganglionic blocking agents chart on 45
 Complex of factors in the human disease introduction 3-4
 Congenital malformations 213
 Congestive heart failure 63 70 73 199 243 243 250-251
 Conjunctivitis 94
 Conn H F 306
 Connell W F 323
 Constriction of renal artery 108
 Constrictor primary amines in the pulmonary circuit 68
 Convulsions 105 121 131
 Cook W J 318
 Cooper A R 318
 Copper 12 83 103 106 113 142 144 144 148 150-151 153 155 157 159 161 167 169 171 175 179 181 193 200-201 207 223 250 251 289
 binding agents 153
 catalyst 223
 chelates 104
 deficiency 172
 in cattle grazing pastures 175
 enzymes 103 148 193
 flavinoid in acyl-coenzyme A-dehydrogenase 147
 in hemoglobin formation 173
 in liver 181
 poisoning 173
 tyrosine 103
 Corcoran A C 212 2164 304 310 313 320 321
 Corley R W 302
 Corn 22, 226 273-280
 composition of 223
 oil 226 273
 Cornea vascularization of 175
 Corned beef 278
 Cornwell D G 523
 Coronary atherosclerosis 213 235-236
 Coronary arterial disease 23 201 203-210 236 269
 Coronary arterial narrowing 238
 Coronary occlusion 3 9 240 243 273 281
 Coronary sclerosis 203-210
 Coronary thrombosis 25 201
 in Ho China 201
 Corrosion of hot water heaters 177
 Cortisone 11 53 136 147 164
 Costello R L 317
 Cottage cheese 280
 Couvet P T 303
 Cottonseed 22, 226 279
 composition of 223
 oil 226 279
 Cotton wool exudate 273
 Council on pharmacy and chemistry 303
 Cousins D H 312
 Cowdry E V 320
 Cows 226
 hypertension in 75
 Cox A J Jr 318
 Cortico-hypothalamic activity 283
 Cortex acidity of 59-59 289 290
 Cortex of the kidney 287
 Cortical steroids 291
 Cox C G 321
 Cream 278 280
 Credner H 303
 Crisco hydrogenated oils III 227
 Crises treatment of 263-276

- D-amino oxidase (histaminase) 50
 63 86
 Diamox 167
 Diaphoresis 34
 Diastolic pressure 3 8 78 107 203
 208 219 246 248 251 255-
 256 262
 effects of metal ions on 107
 Dia.olic hypertension 78 203 208
 246 262
 Diastolic normotension 239 253
 Diarrhea 33-34 174
 Diazine 162
 Dibenamine (derivative of benzyla-
 mine) 45 47 50-51 110
 derivatives 50
 vomiting induced by 51
 Dibenavline 49
 Dicarboxylic acids, 167
 "Diencephalic blush 32 66 285
 "Diencephalic discharge 45
 Dietary experiments on rats 121
 Dietary experiments on monkeys
 121
 Dietary factors altering plasma
 cholesterol in man 226
 Dietary fat relation of to choler-
 terol 223-225
 Dietary salt 153 266 291
 restriction of 291
 Dietary sodium 259
 Diet use of 10-11
 Diffuse dysrhythmias in electroen-
 cephalograms 81
 roentgenologic changes in the
 lungs 81
 Dignals 167 268-270
 Dihydranoquinazoline 86-87
 Dihydroergotamine 110
 Dihydrogen metal 103
 Dihydrogenated ergot alkaloids 48
 Dihydroxyphenylalanine (DOPA)
 62 87 90 97 123 176 179 187
 149 154 207
 Dihydroxyphenylserine 45
 Dilantin 53
 Dilator substances 69
 Dimercaptopropanol (BAL) 83-85
 93 99
 Dimethyl glyoxime 163
 Dimitroff II P., 327
 Dinutrophenol 161 165
 Dinutro-diphenylamine sulfoxide
 163
 Dining J S 312
 Diocaine 165
 Diphenyl 89 163
 carbamide 163
 thiocarbazono 163
 Diphosphochiamin 148
 Dipyrindyl 158
 Disseminated lupus 122
 Disodium dihydrogen versenate 96
 Distension of the intestines 257
 Distiol 163
 Dithiooxalate 163
 Divalent metal disodium ethylene
 diamine tetra acetate 103
 Dixon W. E., 300
 Dizziness 81
 D lysergic acid diethylamide effects
 of on system 35
 DOCA (deoxycorticosterone) 125
 127 133-134 136 291
 Dock W., 370
 Dorfman I 328
 Dogs
 arterial hypertension in 84
 arteritis in 210
 atherosclerosis in 203
 experiments upon 58-62
 Grollman's experiments with 60
 lesions in 16
 nephrectomized 16 60
 neurogenic hypertension in 1, 8
 polycythemia in 172
 renal hypertension in 47 66 73
 106 108 133

- Diamine oxidase (histaminase) 50
 63 86
 Diamox 167
 Diaphoresis III
 Diastolic pressure 3 8 7W 107 203
 908 A 239 246 248 251 255-
 256 962
 effects of metal ions on 107
 Dial. olic hypertension 78 203 208
 246 246
 Diastolic normotension 239 250
 Diarrhea 33-34 174
 Diazine 162
 Dibenzamine (derivative of benzyla-
 mine) 45 47 50-51 110
 derivatives 50
 vomiting induced by 51
 Dibenzylure 48
 Dicarboxylic acids, 160
 "Diacephalic blush 32 68 285
 "Diacephalic discharge 45
 Dietary experiments on rats 121
 Dietary experiments on monkeys
 121
 Dietary factors altering plasma
 cholesterol in man 226
 Dietary fat relation of to chole-
 sterol 223-225
 Dietary salt 130 266 291
 restriction of 291
 Dietary sodium 259
 Diet use of 10-11
 Diffuse dysrhythmias in electroen-
 cephalograms III
 roentgenologic changes in the
 lungs 53
 Digoxin 160 263-270
 Dihydratinoquinazoline 86-87
 Dihydroergotamine 110
 Dihydrogen metal 100
 Dihydrogenated ergot alkaloids 48
 Dihydroxyphenylalanine (DOPA)
 62 87 90 91 123 176 1 0 157
 149 154 207
 Dihydroxyphenylserine 45
 Dilantin 53
 Dilator substances 69
 Dimercaptopropionol (BAL) 83-85
 90 93
 Dimethyl glyoxime 163
 Dimitroff S P. 327
 Dimutrophenol 161 165
 Dimutro-diphenylamine sulfoxide
 163
 Dinning J S 312
 Diocaine 165
 Diphenyl 89 163
 carbamide 163
 thiocarbazono 163
 Diphosphochiamin 148
 Dipyrrolyl 158
 Disseminated lupus 122
 Disodium dihydrogen versenate 96
 Distension of the intestines 257
 Diubol 163
 Diubioxalate 163
 Divalent metal disodium ethylene
 diamine tetraacetate 103
 Dixon W E., 300
 Dizziness 34
 D lysergic acid diethylamide effects
 of on system 35
 DOCA (desoxycorticosterone) 125
 127 133-134 136 291
 Dock W., 300
 Dorfman I 328
 Dogs
 arterial hypertension in 84
 arteritis in 210
 atherosclerosis in 200
 experiments upon 58-62
 Grollman's experiments with 60
 lesions in 16
 nephrectomized 18 60
 neurogenic hypertension in 1, 8
 polycythemia in 172
 renal hypertension in 47 66 73
 106 108 133

- rhythmias in 3°
- Electrolyte abnormality 7° 12> 1°7 139
- Electrolyte imbalance theory of 1,2>1°7
- Electrophoresis 220
- Elliott, D F 303
- Elliott, H III Jr 31°
- Elvehjem C. A 31° 316
- Emaciation 174
- Emboli in the renal artery 24°
- Emerson C A 3°1
- Emesis 7°1
- Emotional tension 249 78>
- Emphysema 219
- Enamels autotomy in 199
- Encephalitis, H
- Encephalopathy (wet brain) 263
- Endocrine organs 4
- Enlarged clitoris 138
- Enlarged heart 8 211
- Enolase 149
- Eureusia, 7 271
- Environment and heredity in arterial hypertension 20-2>
- Enzootic marasmus 174
- Enzymatic deficiencies 20°
- Enzymatic reactions 87 91
- Enzyme systems effect of metal ions on (guinea pig) 1°6
- Epinephrine 40 110 57 58 6> 73 9° 93 133-134 285 289
- Epistaxis 3> 249
- Equanil (2 methyl 2 n propyl 1 3-propanedioldicarbamate) effects of on system 36
- Ergot, derivatives of 119
- Ergotamine 93
- Esbach's reagent 19>
- Esophagus keratinization of in rats 17>
- Esoteric mechanisms 4
- Essential metals in foodstuffs 171 1,6
- Essential metals, sources and turn over of 171 174
- Essential metals in man 166-1,6
- Essential metals in man chart on 169-171
- Esterified cholesterol 216
- Estrogens 236
- Etamon 242
- Ethanol 144
- Ether 16>
- Ethyl (guanylmecapto) acetate hydrochloride 101
- Ethylenediamine tetra acetate (ED TA) III 9> 101 106 126 131 144 150 157 159 16° 1,6 189 193 196 201 230 231 234 240 283 29°
- Ethylene linkages 222
- Ethyl mercaptans 103 187
- Ethyl thiopseudourea group 103
- Etiological factors of atherosclerosis 205 2>1
- Euphoria 90
- Eustachian tube of ear 32
- Evaluation of patient for drug therapy 239 240
- Exacerbation of peptic ulcer 31
- Examples of inhibition of metallo enzymes by metals 152
- Examples of some mammalian metalloenzymes 148 149
- Exanthemata 165
- Excessive drive 285
- Excessive drowsiness 31
- Excessive flushing III
- Excessive proteinuria 159
- Excessive vasomotor tone 13>
- Excitability 191
- Exfoliative dermatitis 16>
- Exogenous cholesterol intestinal absorption of 2°1 222
- Expected results in treatment of atherosclerosis 281 283
- Experimental animals urinary ab

- rhythmias in 3°
- Electrolyte abnormality 7° 12°
1°7 139
- Electrolyte imbalance theory of
1.3-1°7
- Electrophoresis 220
- Elliott, D F 308
- Elliott, H ■ Jr 31°
- Elvehjem C. A 31° 316
- Emaciation 174
- Emboli to the renal artery 24°
- Emerson G A 3°1
- Emesis 7°1
- Emotional tension 249 78°
- Emphysema 219
- Enamel autotomy in 199
- Encephalitis, ■
- Encephalopathy (wet brain) 263
- Endocrine organs 4
- Enlarged clitoris 138
- Enlarged heart 8 211
- Enolase 149
- Eureusia, 7 271
- Environment and heredity in ar
terial hypertension 20-2°
- Enzootic marasmus 174
- Enzymatic deficiencies 20°
- Enzymatic reactions 87 91
- Enzyme systems effect of metal
ions on (guinea pig) 1°6
- Epinephrine 40 ■ 57 58 6° 73
9° 93 133-134 285 289
- Epistaxis 3° 249
- Equanil (2 methyl ■ n propyl 1
3-propanedioldicarbamate) ef
fects of on system 36
- Ergot, derivatives of ■
- Ergotamine 93
- Esbach's reagent 19°
- Esophagus keratinization of in rats
17°
- Esoteric mechanisms 4
- Essential metals in foodstuffs 171
1,6
- Essential metals, sources and turn
over of 171 174
- Essential metals in man 166-1,6
- Essential metals in man chart on
169-171
- Esterified cholesterol 216
- Estrogens 236
- Etamon 242
- Ethanol 144
- Ether 16°
- Ethyl (guanylmecapto) acetate hy
drochloride 101
- Ethylenediamine tetra acetate (ED
TA) 83 9° 101 106 128 131
141 150 157 159 16° 1,6 189
193 196 201 230 231 234 240
283 29°
- Ethylene linkages 222
- Ethyl mercaptans 103 187
- Ethyl thiopseudouracil group 103
- Etiological factors of atherosclerosis
205 2°1
- Euphoria 90
- Eustachian tube of ear 32
- Evaluation of patient for drug ther
apy 239 240
- Exacerbation of peptic ulcer 31
- Examples of inhibition of metallo
enzymes by metals 132
- Examples of some mammalian met
alloenzymes 148 149
- Exanthemata 165
- Excessive drive 285
- Excessive drowsiness 31
- Excessive flushing ■
- Excessive proteinuria 139
- Excessive vasomotor tone 13°
- Excitability 191
- Exfoliative dermatitis 16°
- Exogenous cholesterol intestinal
absorption of 2°1 222
- Expected results in treatment of
atherosclerosis 281 283
- Experimental animals urinary ab

- Frukey R. H., 375
 Frogs, polycythemia in 172
 Fruhgift, M.
 Fruits 177 198
 Fruits juice of 198
 Frying fats 978
 Fulton L. A. 327
 Fundi oculi lesions in 15-16
 Fungicidal chelating agents 157
 Fungicides 173
 Furchgott, R. F., 47 303
 experiments of 47
 Furlenmeier A. 378
 Fisman R. H., 220 322
 Fletcher P. H. 305 314 323
- G**
- Gainsborough 913 215
 Galen H. P. 312
 Gallates 163
 Gallium 161, 179 191
 in the lungs 179 191
 Gallstones metals in 173
 Galvanized zinc 196 198
 Gamma globulins 150
 Ganglionic blocking agents III 54
 105 122 239 244 246-248 252
 257 259 264 266 274 275
 Parenteral 263
 Summary on 53-54
 Ganglionic blockade combined
 therapy with hydralazine 259-
 263 266
 Ganglionic blockade disease 53
 Ganglionic blockade table on side
 effects of 57
 Gangrene
 atherosclerotic 205
 diabetic 204
 senile 204
 Gardner 213 215
 Gann 215
 Gasoline tetra-ethyl lead in 194
 Gastrointestinal disturbances III
- 142 173 180 190 198 249 251
 276
- Gastrectomy 219
 Gastric hyperacidity 33
 Gastric juice 52
 Gastroenteritis 143 198 276
 acute 198
 Gastrointestinal tract, barium in
 180
 Gaudino M., 314
 Gaunt R., 313
 Gelatin 173 198
 Gelhorn E., 300
 Generalized vasospasm exact causes
 of not known 4
 Genest J., 314
 Gertler 215
 Ghose A. C., 212 2164 321
 Gibbons J. E., 301
 Gifford R. W., Jr. 302
 Gilman A. L., III 303 310
 Glass B., 315 318
 Glazer H. S. 311
 Globulin
 bovine 288
 hog, 7 288
 horse 288
 Glomerular capsule thickening of,
 81
 Glomerular filtration 6
 Glomerular obstruction (nephritis
 and glomerulosclerosis) 11 79
 178 129 213 245
 Glomerulonephritis in childhood
 11
 Glossopharyngeal nerve III
 Glucose 8, 97
 Glutamic acid III 76 106 288
 Glutamic decarboxylase 229
 Glutamic dehydrogenase 229
 Glutamic transferase 132
 Glutamine 62-63 107 286 288
 296
 Glutathione 8, 92 97 187

- Frakey R. W., 395
 Frogs, polycythemia in 172
 Fruhgt., 68
 Fruits 179 198
 Fruits juice of 198
 Frying fat 978
 Fulton L. A. 327
 Fundi oculi lesions in 15-18
 Fungoidal chelating agents 157
 Fungicides 173
 Furchgott, R. F., 47 303
 experiments of 47
 Furstenmeyer A. 398
 Fyman R. H., 220 322
 Fitcher W. H. 305 314 325
- G**
- Gainsborough 913 215
 Gale W. P. 312
 Gallates 183
 Gallium 16, 1,9 191
 in the lungs 179 191
 Gallstones metals in 173
 Galvanized zinc 196 198
 Gamma globulins 150
 Ganglionic blocking agents 51 54
 103 122 249 244 246-248 252
 257 259 264 266 274 275
 parenteral 265
 summary on 53-54
 Ganglionic blockade combined
 therapy with hydralazine 260-
 265 266
 Ganglionic blockade disease 53
 Ganglionic blockade table on side
 effects of 57
 Gangrene
 atherosclerotic 205
 diabetic 204
 venous 204
 Gardner 215 215
 Gann 215
 Gasoline tetra-ethyl lead in 191
 Gastrointestinal disturbances 35
 1,2 173 180 190 198 249 251
 276
 Gastrectomy 219
 Gastric hyperacidity 33
 Gastric juice 52
 Gastroenteritis 1,3 198 276
 acute 198
 Gastrointestinal tract, barium in
 189
 Gaudino M., 314
 Gaunt R., 315
 Gelatin 173 198
 Gelhorn E., 300
 Generalized vasospasm exact causes
 of not known 4
 Genest J., 314
 Gertler 215
 Ghose A. C., 212 2164 321
 Gibbons J. E. 301
 Gifford R. W., Jr. 302
 Gilman A. L., 48 303 310
 Glass B., 315 318
 Glazer H. S. 311
 Globulin
 bovine 288
 hog, 7 288
 horse 288
 Glomerular capsule thickening of,
 81
 Glomerular filtration 8
 Glomerular obstruction (nephritis
 and glomerulosclerosis) 11 79
 198 129 213 245
 Glomerulonephritis in childhood
 11
 Glossopharyngeal nerve 88
 Glucose 8, 97
 Glutamic acid 88 76 106 288
 Glutamic decarboxylase 229
 Glutamic dehydrogenase 229
 Glutamic transferase 152
 Glutamine 62,63 10, 285 288
 290
 Glutathione 8, 92 97 187

- Harvey 19
 Hayes F W, 506
 Heart trace metals in 1.0 171
 Hepatic amine oxidase 63
 Hepatic cholesterol 258
 Hepatic chromium 207
 Hepatic lesions 195
 Hepatic metabolism effect of tran-
 sitional metal ions on in rats
 194
 Hepatic synthesis 297
 Hepatitis 51 161 164
 Hepatocellular damage 235
 Hepatomegaly 33 112
 Headaches severe 7 65 91
 Heart burn 55
 Heart disease rheumatic 219
 Heart enlarged 8 241
 Heart failure 3 8 11 23 65 70 73
 181 199 238 241 245 249 251
 268 278-269 297
 congestive 6 70 73 199 245
 245 249-251
 due to ventricular strain 268
 hypertensive 238
 Heart fluoroscopic examination of
 241
 Heart, trace metals in 1.0 171 1.6-
 183 191 196 199
 aluminum in 1.6 183 191 199
 cadmium in 196
 heart, strontium in 199
 Hecht H 11 527
 Hedrick J T, 523
 Heller H 300
 Hellner S 300
 Helmer O 31 301 307 323
 Hematuria microscopic 112
 Hemiplegia 213
 Hemochromatosis 153
 Hemocuprein 147 148
 Hemocyanin 148
 Hemodialysis 118
 Hemodynamics of hypertension 15
 Hemoglobin 173 270
 formation copper in 173
 Heme 147
 Hemorrhage 3 8 13 16 241 242
 247 249 268-271 274 277
 cerebral 271 277
 in the ocular fundi 268
 Hemorrhagic lesions 247
 Hemorrhagic retinitis 15 16 241
 248 270 271
 and exudative retinitis patho-
 genesis of 15 16
 Hepatic 236
 Heredity and environment in ar-
 terial hypertension 20 23 283
 Hess W R, 299
 Hexanoic acids 229 291
 Hexanoic synthesis 229
 Hexamethonium chloride (C₆) 41
 43 53 56 101 103 230 233
 237 256 258 261 263-269 2 0
 271
 effect of as compared with penta-
 pyrrolidinium bitartrate in
 malignant hypertension 259
 intramuscular 265
 Hexamethonium ion 53 101 101
 103
 urinary excretion of 101
 Hexamethylenebis (2 (guanylmethyl-
 capto) ethyl) dimethylammonium
 chloride dihydrochloride
 102
 Hexavalent molybdenum 150
 Hexokinase 149
 Hexosamine 216
 Hexosediphosphatase 149
 Heymans C, 299 302
 Hickham J B 301
 High metabolic activity organs of
 4
 Hillman E C, 18 293
 Hines E A Jr 18 20 298
 Hinkle J A M 300

- Hay fever 19
 Hayes F W., 306
 Heart trace metals in 1,0 171
 Hepatic amine oxidase 63
 Hepatic cholesterol 203
 Hepatic chromium 207
 Hepatic lesions 195
 Hepatic metabolism effect of trans-
 national metal ions on in rats
 194
 Hepatic synthesis 299
 Hepatitis 31 161 164
 Hepatocellular damage 233
 Hepatomegaly 33 112
 Headaches severe 7 66 91
 Heart burn 35
 Heart disease rheumatic 219
 Hearts enlarged 8 241
 Heart failure 3 8 11 23 65 70 73
 191 199 238 241 245 250 251
 266 278-289 297
 congestive 6 70 73 109 243
 245 250-251
 due to ventricular strain 268
 hypertensive 238
 Heart fluoroscopic examination of
 241
 Heart, trace metals in 1,0 171 1,6-
 183 191 196 199
 aluminum in 1,6 183 191 199
 cadmium in 196
 heart, strontium in 199
 Hecht H H 327
 Hedrick J T., 323
 Heller H 300
 Hellner S 300
 Helmer O M 301 307 323
 Hematuria microscopic 112
 Hemiplegia 213
 Hemochromatosis 153
 Hemocuprein 147 148
 Hemocyanins 148
 Hemodialysis 118
 Hemodynamics of hypertension 11
- Hemoglobin 173 270
 formation copper in 173
 Heme 147
 Hemorrhage 3 8 13 16 211 212
 247 249 268-271 274 277
 cerebral 271 277
 in the ocular fundi 268
 Hemorrhagic lesions 247
 Hemorrhagic retinitis 15 16 241
 248 270 271
 and exudative retinitis patho-
 genesis of 15 16
 Heparin 236
 Heredity and environment in ar-
 terial hypertension 20 23 283
 Hess W R., 299
 Hexanoic acids 223 291
 Hexanoic synthesis 299
 Hexamethonium chloride (C₆) 41
 43 53 56 101 103 250 253
 257 258 259 261 263-269 270
 271
 effect of as compared with penta-
 pyrrolidinium bitartrate in
 malignant hypertension 259
 intramuscular 263
 Hexamethonium ion 53 56 101
 103
 urinary excretion of 101
 Hexamethylenebis (2 (guanylmethyl-
 amino) ethyl) dimethylammonium
 chloride dihydrochloride
 102
 Hexavalent molybdenum 150
 Hexokinase 149
 Hexosamine 216
 Hexosediphosphatase 149
 Heymans C., 299 302
 Hickham J B 301
 High metabolic activity organs of
 4
 Hillman C C., 18 293
 Hines E A Jr 18 20 298
 Hinke J A M 303

- in peanut butter 27 27
- H drosha, 153
- Hydrocephalus 213 216
- Hydroxide 13
- Hydroxybenzoic acids, 16
- Hydroxylamine, 70
- Hydroxyl ion, 143 143
- Hydroxyquinoline, 70-71 84, 89
104 147 163-164 230 234
sulfonic acid, 89
- Hydroxytyramine, 29
- Hydroxytryptophan 62, 149
- Hyperaldosteronism, 133 140 232
secondary 136 231
- Hypercholesterolemia, 207 237 232
- Hyperkeratosis in pigs, 175
rats 173
- Hypernatremia, 134
- Hyperpyrexia, 83
- Hyperreflexia, 2 53
- Hypertension—see Angiotensin
- Hypertension
adrenal cortex in, 138
steroids as cause of 133
among American Indians 25
among American Negroes 25
among Hawaiian sugar plantation workers 209
arterial 142 239 281 284 285
293
arterial psychic manifestations
of 284 285
azotemic 60
cadmium as contributing cause
of 192
cerebral role in 33
changes occurring with time in
therapy of 264
clinical implications of, 22-5
130 135 139 140
comment on 25
diastolic 78 203 208 216 246
hemodynamics of, 13
in Africa 25
in China 25 23
in Uganda 25
killing factor in 67
malignant, 24 256 258 260
262-263 270-273
charts on case histories of, 255
5-258 270-273
effect of pentapentadecan,
butyrate in 24 compared
with that of hexamethoni-
um chloride 213
neurogenic, 179 235
seen as form of generalized vaso-
spasm, 4
severe benign 256 258 260-261
some common denominators of
atherosclerosis and, 208-211
syntolic, 203 210
therapy of, 233 276
office practice in, 210-213
practical methods for modern
therapy of 233 276
general rules for 233 276
results expected 268-274
what to do if a patient is not
doing well 264 267
unilateral renal 81 82
- Hypertensive heart failure 258
- Hypertensive kidney 133-139
- Hypertensive patients effect of oral
hydralazine on total fasting
plasma cholesterol in 233
serum sodium of 125
- Hypertensive rats 59 81 95 106
120 177 133 210
experiments upon 59
significant effects on diastolic
blood pressure of EDTA
metal chelates and ion in
106
sodium intake in 127
- Hypertensive states evaluation of
generalized vasospasm in 245
- Hypertensive vascular disease chart

- in peanut butter 27 27
 II drolus, 150
 Hydromephrone 213 210
 Hydroxide, 10
 Hydroxybenzoic acids, 16
 Hydroxybenzamide, 70
 Hydroxyl ion, 143 143
 Hydroxyquinoline, 50-71 84, 89
 104 147 163-164 230 234
 malonic acid, 89
 Hydroxytyramine, 29
 Hydroxytryptophan 62, 149
 Hyperaldosteronism, 133 140 227
 secondary 130 231
 Hypercholesterolemia, 207 237 232
 Hyperkeratosis in pigs, 175
 rats 175
 Hypernatremia, 134
 Hyperpyrexia, 85
 Hyperreflexia, 2 55
 Hypertension—see Angiotonin
 Hypertension
 adrenal cortex in, 133
 steroids as cause of 133
 among American Indians 25
 among American Negroes 20
 among Hawaiian sugar plantation workers 209
 arterial 142 239 281 284 285
 293
 arterial psychic manifestations
 of 281 285
 azotemic 60
 cadmium as contributing cause
 of 192
 cerebral role in 33
 changes occurring with time in
 therapy of 264
 clinical implications of, 22-5
 130 135 139 140
 comment on 20
 diastolic 78 203 208 246 246
 hemodynamics of, 15
 in Africa 25
 in China 25 223
 in Uganda, 25
 killing factor in 67
 malignant, 204 256 258 260
 260-263 270-273
 charts on case histories of, 255
 257 268 270-273
 effect of pentaptyrididin, in
 butyrate in 24 compared
 with that of hexamethonium
 chloride 233
 neurogenic, 129 250
 seen as form of generalized vaso-
 spasm, 4
 severe benign 256 258 260-261
 some common denominators of
 atherosclerosis and, 208-211
 systolic, 203 240
 therapy of, 233 276
 office practice in, 240-243
 practical methods for modern
 therapy of 233 276
 general rules for 233 276
 results expected 268-274
 what to do if a patient is not
 doing well 264 267
 unilateral renal 81 82
 Hypertensive heart failure 258
 Hypertensive kidney 133-139
 Hypertensive patients effect of oral
 hydralazine on total fasting
 plasma cholesterol in 235
 serum sodium of 125
 Hypertensive rats 39 81 95 106
 120 177 133 210
 experiments upon 59
 significant effects on diastolic
 blood pressure of EDPA
 metal chelates and ion in
 106
 sodium intake in 127
 Hypertensive states evaluation of
 generalized vasospasm in 245
 Hypertensive vascular disease chart

- Invertine (metamylamine) 41 43
 270
 Iodine 151
 Ionized calcium 281
 Iproniazid (isonicotinic isopropyl
 hydrazide) 80 89-90 110
 Iron ■ 141 142 147 153 157 167
 175 187 196 201
 ingested, 175
 in the skin 155
 Irritability 194
 Irwin D A 317
 Ischemia 15 18 56 58-61 69 73
 79 87 118 133 139 239 264
 284 286 290
 cerebral, 264
 in kidneys 58-61 ■ 73 79 82,
 133 284 290
 in rabbits ■
 removal of 59-60
 renal organic 127 139 286 288-
 289
 Isoamylamine ■ 99 130 285
 Isocitric, 149
 Isolated rabbit aorta 47 ■ 72
 Isoleucine 74 76
 Isoniazid (isonicotinic acid hydra-
 zide) ■ 86 89 91 100 131
 160 164
 Isopropanol 144
 Isopropyl 83
 Israel comparison of serum lipids
 cholesterol and lipid phospho-
 rus in the old and new immi-
 grants ■ 214
 J ■ M., 310
 Ivy A. C., 323

 J
 Jackson H E., 317
 Jackson R. S 188 324
 Jahn J J 323
 Jam metal in 198
 Janeway T C., 299
 Jarrold T., 311
 Jason R. S 298
 Jastudice 35
 Jeffers W J 300
 Jensen W K., 301
 Johnson A D 305
 Johnson C. A., 307
 Johnson K. D., 322
 Johnson L. L., 312
 Jones R J., 303
 Juxta glomerular apparatus, ■ 129

 K
 Kabra T G 302
 Kahu J R., ■ 307 308
 Kammerer O F., 308
 Kanof A., 310
 Kao K T 328
 Kaplan N D 315
 Karviner E 323
 Katz, L. N., 215 304 320 323 327
 308
 Katzenstein R., 298
 Keith N W 241 247 325
 Kench J E., 195 318
 Keratinization in sheep 175
 Keratinization of the esophagus in
 rats 175
 Kerwin T D 319
 Keto acid carboxylases 148
 Ketogluconic acid, 163
 Keys A., 212 215 322 323 308
 Keys H H 212 215 216A 324
 Kidneys 4 8 8 16 50 57-62 64
 66 68-69 72 74 79 81 83 93
 117 123 125 128 137 133 133-
 139 151 161 170-171 176-183
 187 191 193 194 196-197 199
 200 206 209 219 242 244 273
 206 285
 absence of 60
 amino acids decarboxylated by
 53 64
 cholesterol esterase ■ 128

- Inversine (metamylamine) 41 43
 270
 Iodine 151
 Ionized calcium 281
 Iproniazid (isonicotinic isopropyl
 hydrate) 85 89-90 110
 Iron 83 141 142 147 153 157 167
 173 187 196 201
 ingested, 173
 in the skin 153
 Irritability 194
 Irwin D A 317
 Ischemia 15 16 56 58-61 69 73
 III 87 118 133 139 239 264
 284 286 290
 cerebral, 264
 in kidneys 58-61 69 73 79 82,
 133 284 290
 in rabbits III
 removal of 59-60
 renal organic 127 139 286 288-
 289
 Isoamylamine 62 97 130 283
 Isocitric, 149
 Isolated rabbit aorta 47 69 72
 Isoleucine 74 76
 Isoniazid (isonicotinic acid hydra-
 ride) III 86 89 91 170 181
 167 184
 Isopropanol 144
 Isopropyl 83
 Israel comparison of serum lipids
 cholesterol and lipid phospho-
 rus in the old and new immi-
 grants in 214
 J *in M.*, 317
 Ivy A. C., 323

 J
 Jackson III E., 317
 Jackson R. S 188 324
 Jahn J J 523
 Jam metal in 198
 Janeway T C, 299
 Jarrold T., 311
 Jason R. S 298
 Jaundice 35
 Jeffers W J 300
 Jensen W K., 371
 Johnson A D 305
 Johnson C. A., 307
 Johnson K. D., 322
 Johnson L. L., 312
 Jones R J., 373
 Juxta glomerular apparatus, 60 129

 K
 Kabra T G 302
 Kahu J R., III 307 308
 Kammerer O F., 378
 Kanof A., 310
 Kao K T 328
 Kaplan N D 315
 Karviner E 323
 Katz, L. N., 215 304 320 323 327
 378
 Katzenstein R., 298
 Keith N M 241 247 325
 Kench J E., 195 318
 Keratinization in sheep 175
 Keratinization of the esophagus in
 rats 175
 Kerwin T D 319
 Keto acid carboxylases 148
 Ketogluconic acid, 163
 Keys A., 212 215 322 323 378
 Keys III H 212 215 216A 324
 Kidneys 4 III 8 16 50 57-62 64
 66 68-69 72 74 79 81 83 95
 117 123 125 128 137 133 133-
 139 151 161 170-171 176-183
 187 191 193 194 196-197 199
 200 206 209 219 242 244 273
 276 285
 absence of 60
 amino acids decarboxylated by
 53 64
 cholesterol esters III 128

- in spleen 175-183 193
 in stomach 175-183
 in testes 193
 African 193
 infantile 193
 pipes 195
 poisoning, 161
 virus 194
 Leary T 322
 Lecithin 216 225-227
 Lee R. E., 327
 Le Goff J M 316
 Legumes 172 289
 Lehmann J H., 305
 Lehnninger A. L., 317
 Leiter L., 80 98
 Leloir L. F. 304 308
 Lemieux C 314
 Lemonade cadmium in 193
 L-E phenomenon 113
 Leriche's syndrome 228 282
 Lerner A B 153 313
 Lesions
 arterial, 202 206 237
 at the mucocutaneous junctions 322 326
 cerebral vascular 244
 exudative 247
 found in kidneys 81
 hemorrhagic, 247
 in dogs 16
 in fundi oculi 18 16
 of brain, 31
 organic, 199
 pre atherosclerotic, 293
 pustular 231
 renal inflammatory 243
 sub intimal 293
 traumatic, 212
 vascular inflammatory 243
 Lethargy 271
 Leucine 62-63 74 76 148 152 197
 aminopeptidase 148 152
 Leukemia myeloid, 218
 Leukopenia 112 151 161, 164
 Levere A H 374
 Levine R., 314
 Levitt M F., 314
 Levy R. L. 18 298
 Lewis E., 85 318
 Lewis L. A., 220 313 370 324
 Lewis U J 312
 Lewis W. H., Jr 322
 Lieberman Burchard 210 2164
 Lima beans 289
 Lin T W 323
 Linderholm H., 319
 Linoleate 217 218 278 279
 Linoleic acid foods containing 228
 Linolenic acid 204 222 227 228
 234 279 292, 294 295
 Linseed oil 227
 Lipemic serum 236
 Lipids, 206 213-214 216-217 230
 234 236
 catabolism of 234
 in the blood 206 213 216
 in the liver 230
 plasma 217
 phosphorus 214
 Lipoproteins 210 216 220 221 235
 236 277
 alpha 236
 atherogenic ultra-centrifugal 236
 beta 276
 separated by various techniques
 comparison of 220
 Lipotropic agent 207
 Lisa J R 80 308
 Lithuania 243
 Liver 4 50 63 65 68-69 172 174
 176-183 186 188 189 191 193
 194 196 199 206-208 224 230
 295
 alpha globulins in 221
 cholesterol in 188 221
 cholesterol synthesis by 188
 carbons of 172

- in spleen 176-183 193
 in stomach 176-183
 in testes 193
 African 193
 infantile 193
 pipes 196
 poisoning, 161
 talis 191
 Leary T 322
 Leathin 216 226-227
 Lee R. E., 327
 Le Goff J M 316
 Legumes 172 280
 Lehmann J H., 305
 Lehnunger A. L., 317
 Leiter L., 80 03
 Lelour L. F. 304 308
 Lemieux O 314
 Lemonade cadmium in 193
 L-E phenomenon 113
 Leriche's syndrome 258 282
 Lerner A B 153 313
 Lesions
 arterial, 200 206 237
 at the mucocutaneous junctions
 370 3 8
 cerebral vascular 244
 exudative 247
 found in kidneys 81
 hemorrhagic, 247
 in dogs 16
 in fundi oculi, III 16
 of brain, 31
 organic, 199
 pre atherosclerotic, 293
 pustular 231
 renal inflammatory 243
 sub intimal 293
 traumatic, 212
 vascular inflammatory 243
 Lethargy 271
 Leucine 62-63 74 76 148 152 197
 aminopeptidase 148 152
 Leukemia myeloid, 218
 Leukopenia 112 131 161, 164
 Levere A H 304
 Levine R., 314
 Levitt M F., 314
 Levy R. L. 18 298
 Lewis E., 85 318
 Lewis L. A., 220 313 300 324
 Lewis U J 312
 Lewis W. H., Jr 322
 Lieberman Butchard 210 218 4
 Lima beans 280
 Lin T W 323
 Linderholm H., 319
 Linoleate 217 218 218 279
 Linoleic acid foods containing 228
 Linolenic acid 204 222 227 228
 234 279 292, 294 295
 Linseed oil 227
 Lipidic serum 236
 Lipids, 206 213-214 216-217 230
 234 236
 catabolism of 234
 in the blood 206 213 216
 in the liver 230
 plasma 217
 phosphorus 214
 Lipoproteins 216 216 220 221 235
 236 277
 alpha 236
 atherogenic ultra-centrifugal 236
 beta 206
 separated by various techniques
 comparison of 220
 Lipotropic agent 207
 Lisa J R 80 308
 Lithium 243
 Liver 4 50 63 65 68-69 172 174
 176-183 186 188 189 191 193
 194 196 199 206-209 224 230
 235
 as globulins in III
 cholesterol in 188 224
 cholesterol synthesis by 183
 cirrhosis of 172

Man essential trace metals in 155-176

chart on 170

Man sodium intake in 127

Manganese 72 74 77 83 107 142

147 151 163 154 157 167 169

171 172, 174 179 181 185-187

196 200 201 207-208 234 237
249 257

in urine 172 200

ion 197 1-4

lack of in rabbits, 174

peptidase 77 239

Mann G. V. 321

Mann J. J. G. 31 309

Manometric reflex 240

Maple sugar 171 198

Marasmus emaciated, 174

Margarine 1-3 223 227 278

Mare Strumpell arthritis 231

Marks P. A. 377

Marras J. 80 308

Marsh W. H., 30

Marshall J. 306

Marton R. R. 371 318

Martell A. E. 147 157 314 224

Marius G. J., 372

Mariundale W. E., 330 331

Mason G. V. G. 313

Mayer G., 323

Mayer M. 319

McCorkle W. C. 318

McCubbin J. V. 39 3-3

McDaniel, A. K., 316

McElroy W. H. 315 318

McCall H. C., Jr. 321

McClary D. H., 328

McLean P. H. 300

Meats 177 278

processed, 278

Mecamylamine (Iversine) 41 43

57 53 253 261 270

intoxication, 52

Mechanisms of some of the effects

of chronic arterial hypertension 13 17 203 237

Medoff H. S. 300

Medulla relation of ■ adrenal cortex 133 135

Medulla tumors of 243

Meier R. 26 87 309 377 328

Weilman E., 302

Melster A., 69 327

Melanin 153 202

pigmentation 153

Melnick D. 312

Mendoza R. C., 324

Mendelian dominant vascular reaction to stress as 285

Menhard E. W., 297 305 307 310

Menopause 6 7 233 238

Menstrual abnormalities 137 138

Menses 10 137 138

Mental depression 266

Menthol, 163

Mercaptans 64 65 69 92, 97 99
110 147 150 151 162 194

Mercaptalbumin 147 151 194

Mercaptoethyl hydrogen (carboxy methylmercapto) succinate 99

Mercaptoimidazole 162

Mercaptopropionate 110

Mercaptopropionic acid 89 93

Mercaptopyruvic acid (ammonium salt) 97

Mercaptosuccinic acid 99

Merk Index of Chemicals and Drugs 318

Mercurhydrin 164

Mercusol diuretics 164

Mercury 72 ■ 123 120 143 144
150 153 154 161 193 195 210
268

in kidneys 199

in the skin 153

Merrill A. J., 307

Mesenteric blood flow 48

Metabolism 156

Man essential trace metals in 166-176

chart on 170

Man sodium intake in 127

Manganese 72 74 77 83 107 142

147 151 163 154 157 167 169

171 172, 174 179 181 185-187

196 200 201 207 208 234 257

249 257

in urine 172 200

ion 107 144

lack of in rabbits, 174

peptidase 77 209

Mann G. V. 321

Mann J. J. G. 31 307

Manometric reflex 240

Maple sugar 171 198

Marasmus emaciated, 174

Margarine 143 223 227 278

Mare Strumpell arthritis 231

Marks P. A. 377

Marras J. 80 308

Marsh W. H., 30

Marshall J. 306

Marton R. R. 171 318

Martell A. E. 147 157 314 324

Martus G. J., 372

Martindale W. E., 210 333

Mason G. M. G. 313

Mayer G., 323

Mayer M. 319

McCorkle W. C. 318

McCubbin J. V. 39 343

McDaniel, K. E., 316

McElroy W. D. 315 318

McCall H. C., Jr. 321

McClary D. H., 328

McLean P. H. 300

Meat 177 278

processed, 278

Mecamylamine (Iversine) 41 43
57 53 245 261 270

intoxication, 52

Mechanisms of some of the effects

of chronic arterial hypertension 13 17 203 237

Medoff J. S. 300

Medulla relation of to adrenal cortex 133 135

Medulla tumors of 243

Meier R. 26 87 309 377 328

Meilman E., 302

Meister A., 63 327

Melanin 153 202

pigmentation 153

Meinick D. 312

Mendonça R. C., 324

Mendelian dominant vascular reaction to stress as 285

Menhard E. W., 297 305 307 310

Menopause 67 233 238

Menstrual abnormalities 137 138

Menses 10 137 138

Mental depression 264

Menthol, 163

Mercaptans 64 65 69 92, 97 99

110 147 150 151 162 194

Mercaptalbumin 147 151 194

Mercaptoethyl hydrogen (carboxy methylmercapto) succinate 99

Mercaptolimidazole 182

Mercaptopropionate 110

Mercaptopropionic acid 87 99

Mercaptopyruvic acid (ammonium salt) 97

Mercaptosuccinic acid 99

Merck Index of Chemicals and Drugs 316

Mercuhydria 164

Mercunol diuretics 164

Mercury 72 83 123 130 143 144
150 153 154 161 193 195 210
268

in kidneys 199

in the skin 153

Merrill A. J., 307

Mesenteric blood flow 43

Metacortandren 136

- Morrison H B 317
 Morrison J L 307
 Morrison L M 322
 Morrison M 311
 Morrow J D 101 303 306
 Mortality in hydatid disease 115
 Mortality rates of patients subjected to surgical sympathectomy and chemotherapy chart on 57
 Mosher R E 281 327
 Moshkowitz, L. 80 308
 Moss W G, 300
 Movat H Z 321
 Moy R 11 300
 Mucocutaneous junctional lesions at 175 176
 Mucopolysaccharides 293
 Mucous colitis 251
 Mucous membranes inflammation of 231
 Mueller J 314
 Mueller J F 311
 Mueller J M 308
 Mull J W 317
 Muller J C 301
 Munoz J M 301 308
 Muscle 72 78 138 1,0-171 181 191 196
 stimulant 72
 trace metals in 170-171 181 194 196
 cadmium 196
 lead 194
 tin 181
 titanium 181
 Muscular arteries volume of blood in 78
 Muscular hypertrophy 158
 Mushett C W 321
 Mushrooms vanadium in 185
 Mustard 227
 Mutton 278
 Myalgia 34
 Myeloid leukemia 218
 Myers and Wardell 212 2164
 Myers G B 321
 Myers V C 317
 Mylon E 298
 Myocardial fibrosis 269
 Myocardial infarction 204 218 219 241 275
 Myocardium narrowing of arteries to 132
 Myoglobin 147
- N**
- Narrowing of arteries to brain 132
 Narrowing of arteries in myocardium 130
 Narrowing of arteries renal 190 236
 Nasal congestion 34 249
 Nausea 31 39 48 51 251 266 270
 Najjar V 146 221 313 323
 Nails
 arsenic in 199
 sulfur in 151
 Necropsy 79 81 128
 Necrotizing arteriolar lesions pathogenesis of 16 17
 Negroes American hypertension among 25
 Neligh R. B 300
 Nephrectomy 16 (in 82 210 276
 Nephrectomized dogs 16 60
 Nephrectomized humans 80
 Nephrogenic effector mechanisms clinical observations on 55-68
 drugs acting on 82 109
 hypothesis of 56-57
 Nephritis 129
 Nephron vascular supply in 128
 Nephrosclerotic arteriolar 133 259 269 276-277 286
 as result of hypertension 7 11 (in 128 24, 269 286
 Nephrosis 231

- Morrison D B 317
 Morrison J L 307
 Morrison L M 322
 Morrison M 311
 Morrow J D 101 303 306
 Mortality in hydralazine disease 115
 Mortality rates of patients subjected to surgical sympathectomy and chemotherapy chart on 00
 Mosher R E 281 327
 Moshkowitz, L. 80 308
 Moss W G., 300
 Morat H Z 321
 Moy R J 300
 Mucocutaneous junctions lesions at 173 176
 Mucopolysaccharides 293
 Mucous colitis 251
 Mucous membranes inflammation of 251
 Mueller J 314
 Mueller J F 311
 Mueller J M 308
 Mull J W 317
 Muller J C. 301
 Munoz J M 301 308
 Muscle 72 78 138 1,0-171 181 191 196
 stimulants 72
 trace metals in 170-171 181 194 196
 cadmium 196
 lead 194
 tin 181
 titanium 181
 Muscular arteries volume of blood in 78
 Muscular hypertrophy 138
 Mushett C W 321
 Mushrooms vanadium in 185
 Mustard 227
 Mutton 278
 Myalgia 34
 Myeloid leukemia 218
 Myers and Wardell 212 2164
 Myers G B 321
 Myers V C. 317
 Nylon E 293
 Myocardial fibrosis 269
 Myocardial infarction 204 218 219 241 275
 Myocardium narrowing of arteries to 132
 Myoglobin 147
- N
- Narrowing of arteries to brain 132
 Narrowing of arteries to myocardium 132
 Narrowing of arteries renal 150 236
 Nasal congestion 34 249
 Nausea 31 39 48 51 251 266 270
 Najjar V 146 221 315 323
 Nail
 arsenic in 199
 sulfur in 151
 Necropsy 79 81 128
 Necrotizing arteriolar lesions pathogenesis of 16 17
 Negroes : American hypertension among 25
 Neligh R. B 300
 Nephrectomy 16 60 82 210 276
 Nephrectomized dogs 16 60
 Nephrectomized humans 80
 Nephrogenic effector mechanisms clinical observations on 55-68
 drugs acting on 109
 hypothesis of 56-57
 Nephritis 129
 Nephron vascular supply 128
 Nephrosclerotic arteriolar 133 259 269 276-277 286
 as result of hypertension 7 11 128 24, 269 286
 Nephrosis 231

- Ocular fundi 8 247 252 253 268-
 769
 hemorrhages in 268
 Office practice in therapy of hyper-
 tension 240 243
 Ogden E., 39 303
 Oldt M. R., 297
 Olate 216-217
 Oliguria 262
 Olive oil, 225 227
 composition of, 225
 Olsen N. S., 210 303 306 310 311
 314 378
 Oncley J. L., 325
 O'Neal R. M. 765 297
 Onoma 131
 Opdyke D. F., 578
 Opium 16
 Oppenheim F. 378
 Oppenheimer B. S. 80 308
 Orangeade 193
 Ordway N. K. 318
 Organ E. S., 301
 Organic intra renal arterial and ar-
 teriolar disease 79-81 127 129
 139 241 269 286 288-289
 Organic lesions, 129
 Organic renal disease parenchymal
 79
 Organic renal ischemia 127 248
 288-289
 Organs of high metabolic activity
 4
 Ortho-phenanthroline 158
 Oshry E., 313
 Oster B. L., 312
 Ott, W. H. 378
 Ovarian tumors 244
 Overactivity of the adrenal cortex
 239
 Overman R. R., 315
 Oxalacetate 148
 Oxalic 158
 Oxalosuccinic carboxylase 148
 Oxidation
 as a function of oxygen tension
 chart on relative rate of, 64
 of aldehydes by the liver 174
 of cysteine 181 186
 to its sulfonic acid 184
 of double bond in PFA, 184
 of phospholipid fatty acid 184
 of the amine residues 64-65
 of thioglycolic acid, 184
 Oxidative decarboxation 62
 Oxidative metalloenzymes in kid-
 ney 125
 Oxidized glutathione 103
 Oxygenated Ringer's solution 109
 Oximes, 163
 Oxygen 39 144 145 155 200
 Oxygen consumption of the kidney
 59
 Oxytosis 72 76
 Oysters 173
 Ozone 33
- P
- Page M. D., 297
 Page L. H. 312 313 315 2164,
 220 300 301 303 304 310 313
 370 372 374
 Palladium 144
 Palm oil 278
 Palmitate 216-217
 Palpation of the femoral arteries
 244
 Panagume 164
 P-aminobenzoic acid 162
 P-aminophenol 187
 P-aminosalicylic acid, 162
 Pancreas 4 170-171 176-183 194
 196-197 232 249
 perforation in 249
 trace metals in 170 171 176-183
 194 196
 cadmium 176-183 196

Ocular fundi 8 247 252 258 268-
769

hemorrhages in 268

Office practice in therapy of hyper-
tension 240 243

Ogden E., 39 303

Oldi M. R., 297

Olate 216-217

Oliguria 262

Olive oil, 225 227

composition of, 225

Olsen N. S., 210 303 306 310 311
314 378

Onley J. L., 525

O'Neal R. M., 765 297

Oxonia 151

Opdyke D. F., 578

Opium 165

Oppenheim F. 578

Oppenheimer B. S. 80 308

Orangeade 198

Ordway N. K. 318

Organ E. S., 301

Organic intra renal arterial and ar-
terolar disease 79-81 127 129
133 241 269 286 288-289

Organic lesions, 129

Organic renal disease parenchymal
79

Organic renal ischemia 127 248
288-289

Organs of high metabolic activity
+

Ortho-phenanthroline 158

Oshy M., 315

Oster B. L., 312

Ott, W. H. 378

Ovarian tumors 244

Overactivity of the adrenal cortex
239

Overman R. R., 315

Oxalacetate 149

Oxalic 158

Oxaloacetic carboxylase 148

Oxalosuccinic carboxylase 148

Oxidation

as a function of oxygen tension
that on relative rate of, 64
of aldehydes by the liver 174
of cysteine 181 186
to its sulfonic acid 184
of double bond in PFA, 184
of phospholipid fatty acid 184
of the amine residues 64-65
of thioglycolic acid, 184

Oxidative decarboxylation 62

Oxidative metalloenzymes in kid-
ney 123

Oxidized glutathione 103

Oxygenated Ringer's solution 109

Oximes, 163

Oxygen 39 141 145 155 200

Oxygen consumption of the kidney
59

Oxytocin 72 76

Oysters 173

Ozone 85

P

Pate M. G., 297

Page L. H. III 212 213 215 216A,
220 300 301 303 304 310 313
370 372 374

Palladium 144

Palm oil 278

Palmitate 216-217

Palpation of the femoral arteries
244

Paraquat 164

P-aminobenzoic acid 162

P-aminophenol 187

P-aminosalicylic acid, 162

Pancreas 4 170-171 176-183 194
196-197 232 249

perforation in 249

trace metals in 170 171 176-183
194 196

cadmium 176-183 196

- under anaesthesia 225
- Peritoneal dialysis 60
- Perma Klectr 84 104
- Pernix, 1 4
- Perry B. F., 317
- Perry H. M. Jr 21 85 101 105
107 111 160 183 215 231 233
255 267 270 272 297 301 303
305 307 309 311 317 319 320
324 325 327
- Personality effect of arterial hy-
pertension on 20
- Perustanate 184
- Peters R. A 215 310
- Peterson H. W., 323
- Petroleum formation of 185 187
- Pervanadate 107 188
reduction of by hydralazine 188
- Pervanadyl 92
- PFA
dehydrogenation of 184
oxidation of double bond in 184
- Pharmacological effects of vana-
dium 188
- Phenacetylurea 162
- Phenethylamine
complexes 45-47
derivatives of 45-47
- Phenobarbital 6-7
- Phenolic oxidases 147 173
- Phentolamine (Regitine) 48-49 244
- Phenol red (PSP) 211
- Phenothiazines 184
- Phenurone 164
- Phenylalanine 74 76
- Phenylbutazone 161 162
- Phenyl diazine 88
- Phenyl hydrazine 85
- Phochromocytomata 39 45 49 60
123 214 267
- Phenoxazine 66-75 77 92 103 111
122 288 289
apresoline blockade of 111
in rats 110
- Philips F. S. 310
- Phosphate 117 148 149 151 229
esterification of 229
- Phosphatases 148 149 151
- Phosphoenolpyruvate to ADP 149
- Phosphoglucosmutase 149 152
- Phosphogluconic acid, 149
- Phospholipids 184 186 192 207
217 220 227 235 236 281
anatomic chemistry of 284
fatty acids in 184 207 220
oxidation of 184
of plasma 217
- Phosphonate 143
- Phosphorus 144 199
- Phosphotungstic acid 269
- Phthalazine 88
- Physiological alterations in vascu-
lar volume 78
- Pick, R., 327
- Pickering G. W. 20 21 119 298 299
- Pigmentation 153 173
melanin 153
- Pigs 75 174 175
bone affections in 174
hyperkeratosis in 174
hypertension in 75
- Pijoan M. J. 300
- Pinea K. L., 306
- Piperoxan (Benodaine) 49
- Pitressin 72 92 93 110
- Pitt Rivers R. 318
- Pituitary 27 29 136
basophilism 136
posterior 57
relationship of stalk of to hypo-
thalamus 72
- Pituitaria 72
- Placenta 181 190 191
- Placental membrane 181
- Plants 167 174 190 191 221
metallic content of, 167
sterols of 221
tissues 174 190-191

- under anaesthesia 33
 Peritoneal dialysis 80
 Perma Kicer 84 104
 Pernis, I 4
 Perry B F., 317
 Perry H M Jr 24 33 101 103
 107 111 160 183 215 231 233
 265 267 270 272 297 301 303
 305 307 309 311 317 319 320
 324 325 327
 Personality effect of arterial hy-
 pertension on 20
 Peristanate 184
 Peters R. A. 215 310
 Peterson D W., 323
 Petroleum formation of 185 187
 Pervanadate 107 188
 reduction of by hydralazine 188
 Pervanadyl 92
 PFA
 dehydrogenation of 184
 oxidation of double bond in 184
 Pharmacological effects of vana-
 dium 188
 Phenacetylurea 162
 Phenethylamine
 complexes 45-47
 derivatives of 45-47
 Phenobarbital 6-7
 Phenolic oxidases 147 173
 Phentolamine (Regitine) 48-49 244
 Phenol red (PSP) 211
 Phenothiazines 184
 Phenurone 164
 Phenylalanine 74 76
 Phenylbutazone 161 162
 Phenyl diazine 88
 Phenyl hydrazine 85
 Pheochromocytomata 39 45 49 60
 123 244 267
 Phereytasin 66-75 77 92 109 111
 132 288 289
 apresoline blockade of 111
 in rats 110
 Philips F S 310
 Phosphate 117 148 149 151 229
 esterification of 229
 Phosphatases 148 149 151
 Phosphoenolpyruvate to ADP 149
 Phosphoglucosmutase 149 152
 Phosphogluconic acid, 149
 Phospholipids 184 186 192 207
 217 220 227 235 236 284
 anatomic chemistry of 284
 fatty acids in 184 207 220
 oxidation of 184
 of plasma 217
 Phosphonate 143
 Phosphorus 144 199
 Phosphotungstic acid 269
 Phthalazine 88
 Physiological alterations in vascu-
 lar volume 78
 Pick, R. 327
 Pickering G W 20 21 119 298 299
 Pigmentation 153 173
 melanin 153
 Pigs 75 174 175
 bone affections in 174
 hyperkeratosis in 174
 hypertension in 75
 Pijoan M J 300
 Pines K L., 306
 Piperoxan (Benodaine) 49
 Piretan 72 92 111 110
 Pitt Rivers R. 318
 Pituitary 47 72 136
 basophilum 136
 posterior 57
 relationship of stalk of to hypo-
 thalamus 57
 Pituitaria 72
 Placenta 181 190 191
 Placental membrane 181
 Plants 167 174 190 191 221
 metallic content of, 167
 sterols of 221
 tissues 174 190-191

- in rats 45-46
 Principles of chelation 143 146
 Priscoline (tolazoline) 49
 Privine 93
 Procaine 97 161 164
 amide 161
 salt of β mercaptopropionic acid
 III
 Processed meats 278
 Proctus 231
 Prohormone 148 152
 Proline, 74 76
 Prostate
 carcinoma of, 218 219
 trace metals in 170 171 176-183
 194
 aluminum 176-183
 lead 194
 titanium 176-183
 Prostatic hypertrophy 219 243 257
 Prostatic obstruction 60-61 237
 Prosthetic group 146
 Prostaglandin, III
 Proteins 70 75 157 195 281
 in urine 195
 obtained from renal tissue or
 animal blood 72 75
 Proteinuria 159 176 195 244
 excessive 159
 Proteolytic enzymes 69 148 287
 Protoveratrine III 39 50-51 88 246
 231 257 259 266
 vomiting induced by 51
 Provitamin III 225
 Psoriasis 35
 Psyllium 14 16 39
 Pseudomonas pyocyanus 157
 Pseudopeptidase activity 74
 Pseudothiohydantoin 101
 Psychic manifestations of arterial
 hypertension 284 285
 Psychosomatic disorders 20
 Psychosomatic influences 231
 Psychosomatic summary 284 285
 Psychotherapy III 22 23
 of peptic ulcer 22
 Pious 52
 Pulmonary circuit constrictor pri-
 mary amines in 68
 Pulmonary circulation 67-68
 Pulmonary edema 263
 Pulmonary fibrosis, 193 219
 Pulmonary insufficiency 218 219
 Pulmonary lesions 112
 Pure Food and Drug administra-
 tion 278
 Purkhold, A., 300
 Pustular lesions 231
 Pycelography intravenous 242
 Pycelonephritis (scar) 11 12 79 129
 242 243 245 246 270 273
 during pregnancy 11 12
 Pyloric obstruction III
 Pyrexia 265 271
 Pyrophosphate 187
 Pyocyanus 157
 Pyonephrosis 243
 Pyridine 110
 Pyridazine 261
 Pyridine 85 155 160 163 165
 bases 85
 compound 165
 thiocyanate 163
 Pyridoxal Po., 149 217 228 229 234
 291
 acids 206
 conversion of to its metabolite
 4 pyridoxal acid 90
 deficiency 210 293
 enzymes III 130 176 283
 hydrochloride 91 237
 isoniazid 89 90
 complex in urine 90
 metalloenzyme 293
 phosphate III 130 147
 Pyridoxine 131 176 206 237 278
 280 293
 deficiency 176

- in rats 45-46
 Principles of chelation 143 146
 Prucoline (tolazoline) 49
 Pruvine 93
 Procaine 97 161 164
 amide 161
 salt of β mercaptopropionic acid 97
 Processed meats 278
 Proctus 251
 Prolidase 148 152
 Proline, 74 76
 Prostate
 carcinoma of, 218 219
 trace metals in 170 171 176-183
 194
 aluminum 176-183
 lead 194
 titanium 176-183
 Prostatic hypertrophy 219 243 257
 Prostatic obstruction 60-61 237
 Prosthetic group 146
 Prostagmine, 52
 Proteins 7^o 75 157 195 281
 in urine 195
 obtained from renal tissue or
 animal blood 72 75
 Proteinuria 159 176 195 244
 excessive 159
 Proteolytic enzymes 69 148 287
 Protoveratrine 38 39 50-51 55 246
 251 257 259 266
 vomiting induced by 51
 Provitamin B₁₂ 225
 Prunus 55
Pyo W H., 50₁
 Pseudomonas pyocyaneus 157
 Pseudopeptidase activity 74
 Pseudothiohydantoin 101
 Psychic manifestations of arterial
 hypertension 284 285
 Psychosomatic disorders 20
 Psychosomatic influences 251
 Psychosomatic summary 284 285
 Psychotherapy 6 22 23
 of peptic ulcer 22
 Ptoxis 52
 Pulmonary circuit constrictor pri-
 mary amine in 68
 Pulmonary circulation 67-68
 Pulmonary edema 263
 Pulmonary fibrosis, 195 219
 Pulmonary insufficiency 218 219
 Pulmonary lesions 112
 Pure Food and Drug administra-
 tion 278
 Purkhold, A., 300
 Pustular lesions 231
 Pylography intravenous 242
 Pyelonephritis (scars) 11 12 79 129
 242 243 245 246 270 273
 during pregnancy 11 12
 Pyloric obstruction 23
 Pyrexia 265 271
 Pyrophosphate 187
 Pyrocyanus 157
 Pyonephrosis 243
 Pyridoxamine 110
 Pyridazine 261
 Pyridine 85 155 16^o 163 165
 bases 85
 compound 165
 thiocyanate 163
 Pyridoxal Po., 149 217 228 229 234
 291
 acids 206
 conversion of to its metabolite
 4 pyridoxic acid 90
 deficiency 210 293
 enzymes 62 77 150 176 283
 hydrochloride 91 237
 isoniazid 89 90
 complex in urine 90
 metalloenzyme 293
 phosphate 30 130 147
 Pyridoxine 151 176 206 237 278
 280 293
 deficiency 176

- 20 22
 Reagents for analysis of metals 163
 Red blood cells 4 11
 Refined sugar 1-3
 Refrigerator trays cadmium plated 198
 Regimen effect on plasma cholesterol 282
 Register U D 312
 Regitine (phentolamine) 49 60 110 214
 Reiser M 299
 Reiss H K 373
 Reisman H J 34
 Removal of kidneys 59 61
 ischemic, 59-60
 Removal of tumor 128
 Renal abnormalities, III 73 79
 metabolic by products of 73
 Renal amino acid metabolism 190 291
 Renal amino acid oxidase 63 65
 Renal arteries 7 80 108 127 130 132 205 247 243 286 287
 atheromata of 242 243
 constriction of 108 130 132 286
 diminution of the calibre of 243
 emboli to 242
 external compression of, 243
 intermittent occlusion of, 242
 obstruction mechanical theory of 127 130
 stenosis of 80
 thrombosis of 242
 Renal atherosclerosis 238
 Renal biopsies 81 231
 in dogs, 81
 punch 231
 Renal blood flow 4 41 48 74 208
 Renal circulation effects of nervous discharges upon 57-67
 Renal damage 69
 Renal deaminase 63
 Renal decarboxylase 63
 Renal deficiency 171
 Renal disease 4 16 31 49 159 241
 245 269 246 291
 cardiovascular 291
 organic 159 241 269
 parenchymal 79
 unilateral 276
 Renal disturbances 285 291
 Renal enzymes 61 88 89 203
 mechanisms 208
 systems (guinea pig) effect of metal binding and antihypertensive agents upon 88-89
 Renal excretion of 15 metals before during and after intravenous EDTA 160
 Renal function 246
 Renal hypertension in dogs 17 66 69 70 73 106 108 133
 venous blood of 69 70
 Renal hypertension in rats 101 104 105
 transient effect of dimercaptopropanol (BAL) on systolic pressure of 101
 Renal ischemia 13 39 57 60 63 64 66 70 78 82 117 119 177 129 139 208 211 287 290
 anatomical cause of 78 82
 chronic 290
 organic 288 289
 Renal lesions 19 243
 inflammatory 243
 Renal oxygen consumption 39
 Renal parenchyma 242
 Renal plasma flow 6 93 111 289
 Renal pressor mechanisms 73
 Renal ptosis 212
 Renal sodium wastage 291
 Renal tissue protein obtained from 72 73
 Renal tubular reabsorption of amino acids 195
 Renal tumors 242

- 20 22
 Reagents for analysis of metals 163
 Red blood cells 4 III
 Refined sugar 143
 Refrigerator trays cadmium plated 198
 Regimen effect on plasma cholesterol 282
 Register U D 312
 Regitine (phentolamine) 49 60 110 214
 Reiser M 299
 Reiss O K 373
 Reitman II J 54
 Removal of kidneys 59 61
 ischemic, 59-60
 Removal of tumor 128
 Renal abnormalities, 69 73 79
 metabolic by products of 73
 Renal amino acid metabolism 195 291
 Renal amino acid oxidase 63 65
 Renal arteries 7 III 108 127 150 152 205 247 248 286 287
 atheromata of 242 243
 constriction of 108 150 152 286
 diminution of the calibre of 243
 emboli in 242
 external compression of, 243
 intermittent occlusion of, 242
 obstruction mechanical theory of 127 150
 stenosis of 80
 thrombosis of 242
 Renal atherosclerosis 248
 Renal biopsies 81 231
 in dogs, 81
 punch 231
 Renal blood flow 4 41 48 74 208
 Renal circulation effects of nervous discharges upon 57-67
 Renal damage 69
 Renal deaminase 63
 Renal decarboxylase 63
 Renal deficiency 171
 Renal disease 4 16 III 19 159 211 215 269 246 291
 cardiovascular 294
 organic 159 211 269
 parenchymal 79
 unilateral 276
 Renal disturbances 285 291
 Renal enzymes 61 88 89 203
 mechanisms 208
 systems (guinea pig) effect of metal binding and antihypertensive agents upon 88-89
 Renal excretion of 15 metals before during and after intravenous EDTA 160
 Renal function 216
 Renal hypertension in dogs 17 66 69 70 73 106 108 155
 venous blood of 69 70
 Renal hypertension in rats 101 104 105
 transient effect of dimercaptopropanol (BAL) on systolic pressure of 101
 Renal ischemia 13 39 57 60 63 64-66 70 78 82 117 119 177 129 159 208 III 287 290
 anatomical cause of 78 82
 chronic 290
 organic 288 289
 Renal lesions 19 243
 inflammatory 243
 Renal oxygen consumption 59
 Renal parenchyma 242
 Renal plasma flow C 93 111 289
 Renal pressure mechanisms 73
 Renal ptosis 212
 Renal sodium wastage 291
 Renal tissue protein obtained from 72 73
 Renal tubular reabsorption of amino acids 195
 Renal tumors 212

- diets 259 263 269
 hormones concerned with 136-137
 intake 10-11
 losing kidney 125
 retaining hormone 136
 restriction 137 140
 Samaan A., 293
 Saphir M. 80 303
 Sapirstein L. A. 313
 Saslow G. 293
 Scandium, 191
 Scars (pyelonephritis) 129 132 273
 during pregnancy 11 12
 Schales M. 306
 Scharzenbach 106
 Schiff base 206
 Schizophrenic like states 35
 Scleroderma 201
 Sclerosis M. 80 116 201 203 209-
 210 242
 coronary 209 210
 in autopsies 203
 Sclerotic arteries 56
 Schlutler E., 218 328
 Schlossmann H., 303
 Schneider J. A., 302
 Schoenheimer R. 216 322
 Schreiner A. W., 318
 Schroeder H. A., 24 M. 101 105
 107 111 160 215 218 219 231
 233 251 252 262 267 270 272
 275 297 299 301 303-307 309-
 314 317 319 320 324 327
 Schubert, J. 155 314
 Schuler W. 86-87 309 328
 Schwyzer R. 328
 Schwarz H. J. 307
 Schwartz M. L., 218 219 317
 Scrimshaw N. S. M. 299
 Scrotal inflammation 231
 Scurvy 226
 Sea foods 199
 Sea water 166 180 193
 metals taken from, 67
 percentage of trace metals in
 chart on 168
 Searle N. Z., 315
 Seborrheic dermatitis 131 202 206
 Secondary amine 41
 Secondary effects of hypertension,
 comment on 17
 Sedative drugs M. 33 249
 Sedormid 164
 Seed oils 280
 Seidlin S. M., 315
 Selenium 151 174
 poisoning 174
 Seligmann A. M., 327
 Selling L. S. 301
 Selling P. H. 301
 Selye H., 313
 Semicarbazide HCl 70 87 92 131
 165
 Semmons E., 317
 Senile gangrene 204
 Sequence of development of arterio-
 lar nephrosclerosis 13
 Sequestrene 106 157 164
 Sequestering groups 164
 Serine 76 190
 excretion 190
 Serotonin (derivative of trypto-
 phane) M. 38 67 M. 92, 110
 130 285
 antagonists 33 38
 chart on metabolism of 37
 its effects on system 36
 producing tumor 32
 Serpasil (reserpine) 33 35 50-51
 89 246-252 264
 chart on effect of 250
 Serum
 albumin 196
 beef 76
 cholesterol in 208 221
 horse 74 76
 lipids 214 218-219 236
 lipids iodine number of before

- diets 259 268 *69
 hormones concerned with 136-137
 intake 10-11
 losing kidney 125
 retaining hormone 136
 restriction 137 140
 Samaan A., *99
 Saphir D 80 308
 Sapirstein L. A 313
 Saslow G *98
 Scandium, 191
 Scars (pyelonephritis) 129 132 273
 during pregnancy 11 12
 Schales O 306
 Scharzenbach 106
 Schiff base 206
 Schizophrenic like states 35
 Scleroderma 201
 Sclerosis 56 80 116 201 203 209-
 210 242
 coronary 209 *10
 in autopsies 203
 Sclerotic arteries 56
 Schlittler E., 218 328
 Schlossmann H., 303
 Schneider J A., 302
 Schoenheimer R. 216 322
 Schreiner A. W., 318
 Schroeder H. A., 24 III 101 105
 107 111 160 215 218 219 231
 233 251 252 262 267 270 272
 275 297 299 301 303-307 309-
 314 317 319 320 324 327
 Schubert, J 155 314
 Schuler W 86-87 309 328
 Schwyzer R 3*8
 Schwarz H J 307
 Schwartz P L., 218 219 317
 Scrimshaw N S III 299
 Scrotal inflammation 231
 Scurvy 226
 Sea foods 199
 Sea water 166 185 193
 metals taken from, III
 percentage of trace metals in
 chart on 168
 Searle N Z., 315
 Seborrhoeic dermatitis 131 202 206
 Secondary amine 41
 Secondary effects of hypertension,
 comment on 17
 Sedative drugs 23 33 249
 Sedormid 164
 Seed oils 280
 Seidlin S M., 315
 Selenium 151 174
 poisoning 174
 Seligmann A M., 327
 Selling L. S 301
 Selling P H 301
 Selye H., 313
 Semicarbanide HCl 70 87 92 131
 165
 Semmons E., 317
 Senile gangrene 204
 Sequence of development of arterio-
 lar nephrosclerosis 13
 Sequestrene 106 157 164
 Sequestering groups 164
 Serine 76 195
 excretion 195
 Serotonin (derivative of trypto-
 phane) III 33 6* 68 92, 110
 130 285
 antagonists 33 III
 chart on metabolism of 37
 its effects on system 36
 producing tumor 32
 Serpasil (reserpine) 33 35 50-51
 89 246-252 264
 chart on effect of 250
 Serum
 albumin 196
 beef 76
 cholesterol in 208 221
 horse 74 76
 lipids 214 218-219 236
 lipids iodine number of before

- diets 259 268-769
 hormones concerned with 136-137
 intake 10-11
 losing kidney 12-
 retaining hormone 136
 restriction 137 140
 Samsan A., 299
 Saphir O., 80 308
 Sapirstein L. A. 313
 Saslow G. 298
 Scandium 191
 Scars (pyelonephritis) 129-137 273
 during pregnancy 11 12
 Schaler O. 306
 Scharrenbach 106
 Schiff base 206
 Schizophrenic like states 35
 Scleroderma 201
 Sclerosus 56 80 116 201 203 209-
 210 242
 coronary 209 210
 in autopsies 203
 Sclerotic arteries 111
 Schlittler E., 248 378
 Schlossmann H. 308
 Schneider J. A., 02
 Schoenheimer R. 216 322
 Schreiner A. W., 318
 Schroeder H. A., 94 111 101 105
 107 111 160 215 218 219 231
 233 251 25 262 267 270-272
 275 297 299 301 303-307 309-
 314 317 319-320 324 327
 Schubert J. 155 314
 Schuler W., 86-87 309 328
 Schwytzer R., 323
 Schwarz, H. J. 707
 Schwartz E. L., 218-219 317
 Scrimshaw N. S., 25 299
 Scrotal inflammation 231
 Scurvy 226
 Sea foods 199
 Sea water 186 185 193
 metals taken from 67
 percentage of trace metals in
 chart on 168
 Searle N. Z., 315
 Schorrhaeic dermatitis 131 202 206
 Secondary amine 41
 Secondary effects of hypertension,
 comment on 17
 Sedative drugs 23 11 219
 Sedormid 164
 Seed oils 280
 Seidlin S. M., 315
 Selenium 151 174
 poisoning 174
 Seligmann A. M. 377
 Selling, L. S. 301
 Selling F. H., 301
 Selye H., 315
 Semicarbazide HCl 70 87 92, 131
 165
 Semmons, E., 317
 Senile gangrene 204
 Sequence of development of arterio-
 lar nephrosclerosis 15
 Sequestrene 106 157 164
 Sequestering groups 164
 Serine 76 195
 excretion 19-
 Serotonin (derivative of trypto-
 phane) 32 38 62 111 92 110
 130 285
 antagonists 33 111
 chart on metabolism of 57
 its effects on system 36
 producing tumor 112
 Serpasil (reserpine) 53 35 50 11
 87 246 252 264
 chart on effect of 250
 Serum
 albumin 196
 beef 76
 cholesterol in 208 221
 horse 74 76
 lipids 214 218-219 236
 lipids iodine number of before

- diets 259 268-269
 hormones concerned with 136-137
 intake 10-11
 losing kidney 12
 retaining hormone 136
 restriction 137 140
 Samsan A., 299
 Saphir O., 80 308
 Sapirstein L. A. 313
 Saslow G. 298
 Scandium 191
 Scars (pyelonephritis) 129-137 273
 during pregnancy 11 III
 Schaler O. 306
 Scharrenbach 106
 Schiff base 206
 Schizophrenic like states 83
 Scleroderma 201
 Sclerosis 56 80 116 201 203 209-
 210 242
 coronary 209 210
 in autopsies 203
 Sclerotic arteries 86
 Schlutler E., 248 878
 Schlossmann H. 308
 Schneider J. A., 02
 Schoenheimer R. 216 322
 Schreiner A. W., 318
 Schroeder H. A., 94 III 101 105
 107 111 160 215 218 219 231
 233 251 25 262 267 270-272
 273 297 299 301 303-307 309-
 314 317 319-320 324 327
 Schubert J. 155 314
 Schuler W., 86-87 309 328
 Schwyter R., 528
 Schwartz, H. J. 907
 Schwartz F. L., 218-219 317
 Scrimshaw N. S., 25 299
 Scrotal inflammation 231
 Scurvy 226
 Sea foods 199
 Sea water 166 185 193
 metals taken from 67
 percentage of trace metals in
 chart on 168
 Searle N. Z., 315
 Seborrhoeic dermatitis 131 202 206
 Secondary amine 41
 Secondary effects of hypertension,
 comment on 17
 Sedative drugs 23 III 249
 Sedormid 164
 Seed oils 280
 Seidlin S. W., 315
 Selenium 151 174
 poisoning 174
 Seligmann A. M. 377
 Selling, L. S. 301
 Selling P. H., 301
 Selye H., 313
 Semicarbazide HCl 70 III 92, 131
 165
 Semmons, E., 317
 Senile gangrene 204
 Sequence of development of arterio-
 lar nephrosclerosis 15
 Sequestrene 106 157 184
 Sequestering groups 164
 Serine 76 195
 excretion 19
 Serotonin (derivative of trypto-
 phane) 32 38 62 68 92 110
 130 285
 antagonists 33 III
 chart on metabolism of 37
 its effects on system 36
 producing tumor 32
 Serpaul (reserpine) III 35 50 51
 83 246 252 264
 chart on effect of 250
 Serum
 albumin 196
 beef 76
 cholesterol in 208 221
 horse 74 76
 lipids 214 218-219 235
 lipids iodine number of before

- Sodium 59 83 89 91 92, 99 105
 10⁶ 118 125 127 134 135 141,
 186-188 244 246-247 259 261
 262 286 288-289 291
 amyral 244 246-247
 release test, 244
 azide (NaN₃) 83 89 92 259 261
 content of arterial walls, 125
 cyanide 89
 dietary 259
 intake in hypertensi = rats 127
 intake in man 127
 loss by kidneys 291
 metavanadate 186 188
 nitroprusside ■ 89 94
 pertitanate 187
 potassium 291
 thiocyanate 89 106 108
 slow deficiency in 173 175
 cobalt, 174 175
 nitrogen 174
 Sulfers anionomy in 199
 Soley M J 315
 Sollmann T 91 316
 Solomon C., 80 303
 Soluble complexes of thiocyanates
 in water 93
 Soluble salts 91
 Somogyi zinc method 259 269
 Somogyi zinc precipitate 269
 Soups
 canned 198 280
 meat 199 289
 Sources and turnover of essential
 metals 171 173
 Soybeans 171 186 227 279 280
 lecithin 186
 total blade of 173
 oil from 279 280
 Spackman D J 312-319
 Spasm 342
 "spasmi, by
 Specific metal deficiencies 174 176
 specific nephrogenic effector sub-
 stances 68-71
 Specific use of drugs ■ 38-39 41
 ■ 248 267
 used in therapy of hypertensive
 patients 33 41 54
 used in therapy of ■ effecting
 ganglia 41 54
 used in therapy of effecting carotid
 sinus 38-39
 Speer F D., 310
 Spence E. R., 312
 Spinal fracture 218
 Spinnagel J 309
 Splanchnic bed 65
 Splanchnic blood flow 41
 Spleen 4 140 171 176 183 191 192
 194 196
 trace metals in 170 171 176-183
 191 192 194 196
 aluminum 191
 boron 176-183
 cadmium 196
 lanthanum 180
 lead 176 183 191
 Mn 181 192
 Splenomegaly 112
 Squalene (C₃₀H₅₀) 224 225 292
 Stamler J 215 313 327
 St Andre & F 319
 Stanley M 314
 Staphylococcus aureus 157
 State F J 321
 Starling E. H 300
 Starvation 226
 Stearate 210 216-217
 Stearic acid 222
 Steele J M 299 301 325
 Steiner A 323
 Steiner R. L. 314
 Steiner R. S 316
 Stewart, C. P., 80 212 308
 Stewed apples 193
 Steyermark, P., 314
 Stenosis of renal arteries 80

- Sodium 80 83 89 91 93 99 105
 106 118 123 127 134 135 141,
 186-188 244 246-247 259 261
 262 286 288-289 291
 amylal 244 246-247
 release test, 244
 azide (Na_3N_3) 83 89 93 259 261
 content of arterial walls, 125
 cyanide 89
 dietary 259
 intake in hypertensi = rats 127
 intake in man 127
 loss by kidneys 291
 metavanadate 186 188
 nitroprusside 83 89 94
 pernitrate 187
 potassium 291
 thiocyanate 89 106 108
 toxic deficiency in 173 175
 cobalt, 174 175
 nitrogen 174
 sulfur antimony in 199
 Soley M J 313
 Sollmann T 91 316
 Solomon C., 80 303
 Soluble complexes of thiocyanates
 in water 80
 Soluble salts 91
 Somogyi zinc method 259 269
 Somogyi zinc precipitate 269
 Soups
 canned 193 280
 meat 193 280
 Sources and turnover of essential
 metals 171 173
 Soybeans 171 186 227 279 280
 lecithin 186
 meal made of 171
 oil from 279 280
 Spackman D J 312-313
 Spasm 242
 Spanish, 59
 Specific metal deficiencies 174 176
 specific hypotensive effector sub-
 stances 58 71
 Specific use of drugs 31 38-39 41
 31 248 267
 used in therapy of hypertensive
 patients 33 41 54
 used in therapy of effecting
 ganglia 41 54
 used in therapy of effecting carotid
 sinus 38-39
 Speer F D., 310
 Spence E. R., 312
 Spinal fracture 318
 Spinnagel J 309
 Splanchnic bed 63
 Splanchnic blood flow 41
 Spleen 4 170 171 176 183 191 192
 194 196
 trace metals in 170 171 176-183
 191 192 194 196
 aluminum 191
 boron 176-183
 cadmium 196
 lanthanum 180
 lead 176 183 191
 iron 181 192
 Splenomegaly 112
 Squalene ($\text{C}_{30}\text{H}_{50}$) 224 225 292
 Starbier J 215 313 327
 St Andre & F 319
 Stanley M 314
 Staphylococcus aureus 157
 State F J 321
 Starling E. H 300
 Starvation 226
 Stearate 210 216-217
 Stearic acid 222
 Steele J M 299 304 325
 Steiner A 323
 Steiner R. L. 314
 Steiner R. S 316
 Stewart, C. F., 80 212 308
 Stewed apples 193
 Steyermark, P., 314
 Stenosis of renal arteries 80

Sympathetic nervous mechanisms
through ganglia 39 54
Sympatholytic drugs response to
55
Sympathomimetic amines 50
Sympathotonic people diseases sub
ject to 19
Synaptic transmission 32
Syncope 34 270
Synthesis of cholesterol from ace
tate 184
Synthesis of fatty acids from acetate
184
Syphilis 188 243
Systolic hypertension 203 240
Systolic pressure 203 255 262 263
Szent-Györgyi A 117 311

T

Table on actions of adrenergic
blocking agents in man 43
Table on side effects of ganglionic
blockade 52
Tachycardia 7 34 35 48 93 127
259 265
Tachypnea sign of ganglionic block
ade disease 53 265
Tallow 278
Tanning 209
Tapazole 99 161 162
Tappan H V 312
Taqui A C, 308
Tartaric acid 198
Tartrate 158
Taylor B 308
Taylor H L, 325
Taylor R, D 300 310 315
Tea 171 173
Teart, 174
Technetium, 151
Teitelbaum H 317
Tellurium 151
Terminal carboxyl 75 77
decarboxylation of 75

Terpenes 224
Terramycin 157
Tertiary amines 46
Tertiary compounds 32
Testis trace metals in 1 0-171
Testicular tumors 211
Testosterone 236
Tetravalent nitrogen 40-41 44
Tetraethenoid acids, 228
Tetra-ethyl ammonium chloride
(Etixon) 6 9 43 242
Tetra ethyl ammonium ion 8 41
56
Tetra-ethyl lead in gasoline 191
Tetrasodium pyrophosphate 81 89
Tetrathiodiacetic acid 101
Tetrahedral chelates 144 146
Thallium 167 180
Theory of depletion of vascular
substances 117 118
Theory of electrolyte imbalance
125 127
Theory of habitual repetitive stim
uli 117
Theory of local vitamin B defi
ciency 120-121
Theory of mechanical renal arterial
obstruction 127 130
Therapeutic pressure as secret of
successful therapy 264
Therapy of Hypertension
office practice in 240-243
practical methods for 233 276
general rules for 238 276
results expected 268 274
successful continuous therapeutic
pressure as secret of 261
Thiadiazole 169 165
Thiamine 147
Thickening of glomerular capsule
81
Thickening of the walls of the ar
terioles 128
Thon skin 133

Sympathetic nervous mechanisms
through ganglia 39 34
Sympatholytic drugs response to
55
Sympathomimetic amines 20
Sympathotonic people diseases sub
ject to 19
Synaptic transmission 32
Syncope 34 270
Synthesis of cholesterol from ace
tate 184
Synthesis of fatty acids from acetate
184
Syphilis 188 243
Systolic hypertension 203 240
Systolic pressure 253 255 262 263
Szenti-György A 117 311

T

Table on actions of adrenergic
blocking agents in man 48
Table on side effects of ganglionic
blockade 52
Tachycardia 7 34 35 48 93 127
239 263
Tachypnea sign of ganglionic block
ade disease 53 263
Tallow 278
Tanning 209
Tapazole 99 161 162
Tappan D V 312
Tagumi A C., 309
Tartaric acid 196
Tartrate 158
Taylor B 308
Taylor H L., 325
Taylor R. D 300 310 313
Tea 171 173
Tear, 174
Technetium, 151
Teitelbaum S 317
Tellurium 151
Terminal carboxyl 75 77
decarboxylation of 75

Terpenes 224
Terramycin 157
Tertiary amines 46
Tertiary compounds 32
Testis trace metals in 1 0-171
Testicular tumors 211
Testosterone 236
Tetravalent nitrogen 40-41 44
Tetraethenoid acids, 228
Tetra-ethyl ammonium chloride
(Etamon) 6 9 43 242
Tetra ethyl ammonium ion 8 41
56
Tetra-ethyl lead in gasoline 191
Tetrasodium pyrophosphate 81 89
Tetrathiodiacetic acid 101
Tetrahedral chelates 144 146
Thallium 167 180
Theory of depletion of vascular
substances 117 118
Theory of electrolyte imbalance
125 127
Theory of habitual repetitive stim
uli 117
Theory of local vitamin B defi
ciency 120-121
Theory of mechanical renal arterial
obstruction 127 130
Therapeutic pressure as secret of
successful therapy 264
Therapy of hypertension
office practice in 240-243
practical methods for 238 276
general rules for 238 276
results expected 268 274
successful continuous therapeutic
pressure as secret of 261
Thiadiazole 169 165
Thiamine 147
Thickening of glomerular capsule
81
Thickening of the walls of the ar
terioles 128
Thunberg 138

- abnormal 99
 and cardiovascular disease 141
 202
 and pyridoxal 229-235
 clinical implications of 200-202
 essential concentrations of in
 man 167 169-171
 chart on 1,0
 found in sea water % chart on
 163
 in man probable roles of chart
 on 167
 in adipose tissue 1,0 171
 in adrenal 123 1,0 171 1,6 183
 194 196
 in aorta 1,0-171 176-183
 in bladder 170 171 176-183 194
 in blood vessels 123
 in brain 123 170 171 1,0-183
 191 193 194 196
 in heart, 1,0 171
 in intestines 1 0 171 181 194
 196
 in kidney 83 121 123 125 154
 170-171 176-183 191 193 194
 196 197 199 290
 in liver 69 193 170-174 176 183
 186 188-189 191 193 194 196
 199 203 224 230
 in lungs 53 67-68 170 171 176
 183 187 189 191 194
 in muscle 170 171 181 191 196
 in pancreas 170 171 176 183 194
 196
 in prostate 170 171 1 6-183 194
 in skeleton 170 171
 in skin 153 170-171 200
 in spleen 170-171 176-183 191
 197 194 196
 in stomach 170-171 176-183 196
 in testis 170 171
 in thyroid 170, 173
 in tissues 1,0 171 180 185 280-
 281 283
 from uncivilized peoples 182
 183
 infants 180 183
 in urine 101 113 122 123 163
 172 189-190 192 193 193 200
 imbalance 121 123 237
 Tranquilizers 33 285
 Tranquilizing action of reserpine
 33
 Transaminase 149 283
 Transient effect of dimercaptopro-
 panol (BAL) on systolic pres-
 sure of renal hypertensive rat
 101
 Transition from intermittent to
 permanent vasospasm 116-140
 metals as cause of 144
 Transphorylase 149
 Trauma 2,6
 Traumatic lesions 242
 Treatment of atherosclerosis pre-
 liminary approach to 277 283
 Treatment of crises 263 276
 Tremulousness 34
 Tremors in dogs 53
 Tri-decyl mercaptan 99
 Triglycerides 222
 Tri-nephaphan camphor sulfonate
 structural formulae of 42
 Tripod J 87 309 423
 Treadium EDTA 281
 Tribione (SKF 1717) 102 107
 Trivalent iron 105
 Trujillo T T 316
 Trypsin 71
 Tryptamine 62 84 126 130
 Tryptophane 35 37 62
 Tsalas T T 323
 Tuberculous 90 183
 Tucker H F 316
 Tulipule P G 223
 Tumors 19 31 32 61 148 202,
 247 244
 adrenal cortical 243

- abnormal 209
 and cardiovascular disease 141
 202
 and pyridoxal 229-235
 clinical implications of 200-202
 essential concentrations of in
 man 167 169-171
 chart on 1,0
 found in sea water % chart on
 163
 in man probable roles of chart
 on 167
 in adipose tissue 1,0 171
 in adrenal 125 1,0 171 1,6 183
 194 196
 in aorta 1,0-171 176-183
 in bladder 170 171 176-183 191
 in blood vessels 125
 in brain 125 170 171 1,6-183
 191 195 196 196
 in heart, 1,0 171
 in intestines 1 0 171 181 191
 196
 in kidney 83 121 123 123 154
 170-171 176-183 191 193 194
 196 197 199 200
 in liver 69 1,0 170-171 176 183
 186 188-189 191 193 194 196
 199 200 204 230
 in lungs 53 67-68 170 171 176
 183 187 189 191 194
 in muscle 170 171 181 191 196
 in pancreas 170 171 176 183 194
 196
 in prostate 170 171 1 6-183 191
 in skeleton 170 171
 in skin 153 170-171 200
 in spleen 170-171 176-183 191
 197 194 196
 in stomach 170-171 176-183 196
 in testis 170 171
 in thyroid 170-171
 in tissues 1,0 171 180 185 280-
 281 285
- from uncivilized peoples 182
 183
 infants 180 183
 in urine 101 113 122 123 163
 172 189-190 192 193 193 200
 imbalance 121 123 237
 Tranquilizers 35 285
 Tranquilizing action of reserpine
 33
 Transaminase 149 283
 Transient effect of dimercaptopro-
 panol (BAL) on systolic pres-
 sure of renal hypertensive rat
 101
 Transition from intermittent to
 permanent vasospasm 116-140
 metals as cause of 144
 Transphorylase 149
 Trauma 2,6
 Traumatic lesions 242
 Treatment of atherosclerosis pre-
 liminary approach to 277 '83
 Treatment of crises 263 '76
 Tremulousness 34
 Tremors in dogs 63
 Tri-decyl mercaptan 99
 Triglycerides 222
 Trimethaphan camphor sulfonate
 structural formulae of 42
 Tripod J 87 309 423
 Trisodium EDTA 281
 Trisibone (SKF 1717) 102 107
 Trivalent iron 103
 Trujillo T T. 316
 Trypan 71
 Tryptamine 62 III 126 130
 Tryptophane 36 37 62
 Tuskas T T 323
 Tuberculous 90 188
 Tucker H F 316
 Tulipule P C '23
 Tumors 19 31 32 61 148 202,
 247 244
 adrenal cortical 243

- volume 150 241
 concentration test, 241
 Urticaria 19 165
 Uterine prolapse 245
 V
 Vagal stimulation, 39
 Value 74 76
 Vallee B L, 315 319
 Vanadium 67-68 113 142 144 150
 159 167 180 183 185 188 191
 197 203 283 292
 acetate 186
 deficiency 188 285
 evidence for its being essential
 trace metal, 187 188
 in the lungs 68 180
 in therapy of degenerative cardio-
 vascular diseases 191
 pharmacological effects of 188
 urinary output of, 188
 Vanadyl ion 153
 Van Slyke D D 322
 Various effects of pyridoxine in
 man chart on 131
 Vasa vasorum 205
 Vascular constriction 72
 Vascular disease cerebral 284
 peripheral 281 282
 Vascular hyperreactivity 138
 Vascular lesions 32 35 56 119 133
 243
 in the hypothalamus 113 114
 inflammatory 243
 Vascular substances theory of de-
 pletion of 117 118
 Vascular tumor of brain 219
 Vascular volume physiological al-
 terations in VII
 Vascularization of the cornea 175
 Vasoactive amines 60 291
 Vasoactive peptides 60 76 110
 adrenergic blockade of 110
 amino acids in chart on 76
 Vasoactive polypeptide 85
 Vasoactive substances found in
 blood, 73
 Vasoactive substances found in
 urine 73
 Vasoconstriction 49 50 57 183
 in rabbits 188
 Vasodilatation 3 41
 Vasodilating drug 41
 Vasoexcitator material (VEM) 58-59
 73 78
 Vasomotor tone effect of brain on
 50
 Vasomotor tone excessive 135
 Vasopressin 72 76
 from hogs, 6
 Vasospasm 3 18 20 22 55 77 215
 lability of 215
 reaction to stress by 18 20 22
 Vasospastic states acute 77
 Veal 279
 Vegetables 172 185 190 198 222
 223 226-227 233 277
 cadmium in 198
 chromium in 185
 fats 222 223 226-227 233 277
 oils 190 222
 VEM (vaso-excitator material) 58 59
 73 78
 Venous pressure 52 69
 Ventricular strain heart failure
 due to 263
 Versene (see EDTA) 157
 Vertigo 270
 Vier M 315
 Vilter R. W. 309 311 318
 Vinegar 193
 Vinogradov A P 168 316
 Viscus hollow 257
 Vision blurred 7 35
 Vitamins, A 221
 B 90 95 119 121 131 191 197
 202 206-207 209 211 216
 226 227 229 230 234 235 237

- volume 160 241
 concentration test, 241
Urticaria 19 165
Uterine prolapse 243
 V
Vagal stimulation, 39
Valine 74 76
Vallee B. L., 315 319
Vanadium 67-68 83 142 144 150
 159 167 180 183 185 188 191
 197 208 283 292
 acetate 186
 deficiency 188 285
 evidence for its being essential
 trace metal, 187 188
 in the lungs 68 180
 in therapy of degenerative cardio-
 vascular diseases 191
 pharmacological effects of 188
 urinary output of, 188
Vanadyl ion 153
Van Slyke D. D. 322
 Various effects of pyridoxine in
 man chart on 181
Vasa vasorum 205
Vascular constriction 72
Vascular disease cerebral 284
 peripheral 281-282
Vascular hyperreactivity 138
Vascular lesions 32 33 56 119 133
 243
 in the hypothalamus 32 33
 inflammatory 243
Vascular substances theory of de-
 pletion of 117 118
Vascular tumor of brain 219
Vascular volume physiological al-
 terations in 78
Vascularization of the cornea 175
Vasoactive amines 60 291
Vasoactive peptides 60 76 110
 adrenergic blockade of 110
 amino acids in chart on 76
Vasoactive polypeptide 69
Vasoactive substances found in
 blood, 73
Vasoactive substances found in
 urine 73
Vasoconstriction 49 50 57 183
 in rabbits 183
Vasodilatation 3 41
Vasodilating drug 41
Vasoexcitator material (VEM) 58-59
 73 78
Vasomotor tone effect of brain on
 30
Vasomotor tone excessive 135
Vasopressin 72 76
 from hogs 46
Vasospasm 3 18 20 22 53 77 215
 lability of 215
 reaction to stress by 18 20 22
Vasospastic states acute 77
Vcal 279
Vegetables 172 185 190 198 222
 223 226-227 233 277
 cadmium in 198
 chromium in 185
 fats 222 223 226-227 233 277
 oils 190 222
VEM (vaso-excitator material) 58 59
 73 78
Venous pressure 52 69
Ventricular strain heart failure
 due to 263
Versene (see EDTA) 157
Vertigo 270
Vier H. 315
Vilter R. W. 309 311 318
Vinegar 193
Vinogradov A. N. 168 316
Viscus hollow 257
Vision blurred 7 35
Vitamins, A 221
 B 90 95 119 121 131 194 197
 202 206-207 209 211 216
 226 227 229 230 234 235 237

- Yeast 143
 Yule C. L. III 309
- Z
- Zack B 304
 Zawonski E J 303
 Zeller W W 34 307
 Zinc 79 84 94 95 104 105 107
 113 120 123 125 131 142 144
 147 150 151 153 154 157 159
 161 167 169 171 173 175 176
 181 193 195 201 237 238
 chelates 104
 coating, 196
 deficiency 95 120 131 175-176
 foil 198
 in foods 198
 metalloprotein 150
 poisoning 199
 reagent III III
 Zirconium 180
 Zumer N., 315
 Zlathis A., 324
 Zona glomerulosa 138 292
 Zondek S. G., 293
 Zucker M B 303
 Zweifach B W., 303 304 310 314
 320 322

Yeast 143
 Yule C. L. 81 309

Z

Zack B. 304
 Zawonski E. J. 303
 Zeller W. W. 34 309
 Zinc 79 84 94 95 101 103 107
 113 110 123 125 131 142 144
 147 150 151 153 154 157 159
 161 167 169 171 173 175 176
 181 193 195 201 239 288
 chelates 104
 coating, 196

deficiency 93 110 131 175-176
 foil 198
 in foods 198
 metalloprotein 150
 poisoning 199
 reagent 84 94
 Zirconium 180
 Zimmer N., 315
 Zlathus A., 324
 Zona glomerulosa 138 292
 Zondek S. G., 298
 Zucker M. B. 303
 Zweifach B. W., 303 304 310 314
 320 322



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HENRY ALFRED SCHROEDER M D F.A.C.P

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